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Atypical post-infectious glomerulonephritis is associated with abnormalities in the alternative pathway of complement

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Abstract

Post-infectious glomerulonephritis is a common disorder that develops following an infection. In the majority of cases, there is complete recovery of renal function within a few days to weeks following resolution of the infection. In a small percentage of patients, however, the glomerulonephritis takes longer to resolve resulting in persistent hematuria and proteinuria, or even progression to end-stage kidney disease. In some cases of persistent hematuria and proteinuria, kidney biopsies show findings of a post-infectious glomerulonephritis even in the absence of any evidence of a preceding infection. The cause of such ‘atypical’ post-infectious glomerulonephritis, with or without evidence of preceding infection, is unknown. Here, we show that most patients diagnosed with this ‘atypical’ post-infectious glomerulonephritis have an underlying defect in the regulation of the alternative pathway of complement. These defects include mutations in complement regulating proteins and antibodies to the C3 convertase known as C3 nephritic factors. As a result, the activated alternative pathway is not brought under control even after resolution of the infection. Hence, the sequela is continual glomerular deposition of complement factors with resultant inflammation and development of an ‘atypical’ post-infectious glomerulonephritis.

Keywords

post-infectious glomerulonephritis; persistent glomerulonephritis; alternative pathway of complement; C3 glomerulonephritis; membranoproliferative glomerulonephritis

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INTRODUCTION

Post-infectious glomerulonephritis is a type of glomerulonephritis seen in both children and adults following an infection. The glomerulonephritis is manifested by development of a nephritic syndrome within 1–3 weeks of an infectious episode.^{1–3} The infection is often mild and typically resolves by the time the glomerulonephritis is diagnosed. The pathogenesis of post-infectious glomerulonephritis is thought to be due to (1) glomerular in-situ deposition of bacterial antigens with subsequent antibody build-up and formation of in-situ immune complexes and/or (2) glomerular deposition of circulating immune-complexes.^{2–6}

The characteristic features of post-infectious glomerulonephritis on kidney biopsy are a proliferative glomerulonephritis on light microscopy (LM), bright C3 staining with or without immunoglobulins on immunofluorescence (IF) microscopy, and subepithelial deposits called ‘humps’ on electron microscopy (EM).^{3, 7, 8} It should be pointed out that in some cases the diagnosis of post-infectious glomerulonephritis is made based on these biopsy findings even in the absence of any clinical, bacterial or serological evidence of a preceding infection.

The majority of patients achieve complete remission of the nephritic syndrome following post-infectious glomerulonephritis. However, in a small percentage the disease takes longer to resolve or persists with renal dysfunction evidenced by continuing hematuria and proteinuria. A smaller percentage still progresses to end-stage kidney disease.^{1, 4, 7–10} The terms ‘persistent’, ‘resolving’ or ‘chronic’ post-infectious glomerulonephritis have been used to describe these entities.

During an infection that triggers development of post-infectious glomerulonephritis, there is activation of the AP of complement.^{4, 11, 12} Following elimination of the infection, immune-complexes are cleared, AP activity is controlled, and glomerulonephritis resolves.^{11, 13} We hypothesized that in patients who take longer to resolve, develop persistent proteinuria and hematuria, or progress to end stage kidney disease there is a defect in the regulating mechanisms of the AP of complement that prevents its down-regulation following resolution of the infection. The consequence is excessive deposition of complement proteins and breakdown products in the glomeruli seen as the pathognomonic bright C3 staining on IF microscopy on kidney biopsy. An inflammatory response ensues with the development of persistent proliferative glomerulonephritis. We define such cases as ‘atypical’ post-infectious glomerulonephritis, to highlight the presence of an abnormality in the AP of complement. To test this hypothesis, we evaluated the AP of complement in 11 patients with persistent hematuria and proteinuria diagnosed with post-infectious glomerulonephritis on kidney biopsy to determine whether an underlying abnormality of AP of complement could be identified. The study included 6 cases with a kidney biopsy diagnosis of post-infectious glomerulonephritis even though there was no evidence of a preceding infection.

RESULTS

Clinical Findings (Table 1)

Our study included 11 patients who fulfilled the diagnostic criteria of 'atypical' post-infectious glomerulonephritis. The diagnostic criteria of 'atypical' post-infectious glomerulonephritis were as follows: 1) Persistent hematuria and proteinuria, with or without history of preceding infection; 2). Renal biopsy showing features of post-infectious glomerulonephritis- a) Proliferative glomerulonephritis on LM, including patterns of diffuse or focal endocapillary proliferative and exudative glomerulonephritis, and mesangial proliferative glomerulonephritis; b) Mesangial and/or capillary wall C3 with or without immunoglobulin staining on IF microscopy; c). Subepithelial 'hump-like' deposits on EM. 3) Abnormalities of the AP of complement.

All of the 11 patients were evaluated at the Mayo Clinic, 9 of whom were referred to the Mayo Clinic from an outside institution when renal function did not improve or there was persistent hematuria and proteinuria. In 5 of the 11 patients, there was a history of upper respiratory tract infection, while one patient (patient #9) had an upper respiratory infection and impetigo. In the remaining six, it was not clear from the outside records if there had been an antecedent illness. The upper respiratory illnesses varied from 4 days to 1 month prior to development of kidney disease. Time from development of kidney disease to kidney biopsy varied from 2 weeks to 15 months (mean 4.1 months), although in one case (patient #3) the biopsy was done 1 day after development of kidney disease. There were 5 females and 6 males (age range, 2 to 71 years; mean, 35.1 years), including 1 child, 2 teenagers, and 8 adults. The serum creatinine at presentation ranged from 0.5 mg/dL to 3.1 mg/dL (mean, 1.4 mg/dL), with an estimated glomerular filtration rate of 16 to 109 ml/minute (mean 58 ml/minute/1.73m²). The serum creatinine at time of biopsy ranged from 0.5 to 3.1 mg/dL (mean 1.5 mg/dL). Ten patients were hypertensive and 10 had documented hematuria. Twenty-four hour urinary protein ranged from 500 to 15760 mg/24 hours (mean, 5139 mg/24 hours). C3 levels were low in 7 patients, with a range of 3 to 135 mg/dL (mean, 64.3 mg/dL; normal range 80–175 mg/dL) while it was within normal in 4 patients. C4 levels were normal in all patients. Platelet counts were low in patient #1 while they were normal in all other patients. Schistocytes were absent on the peripheral smear in patient #1. Hemoglobin levels ranged from 7.9 to 14.3 gms/dL (mean 11.1 gms/dL). ASO titers at presentation at the Mayo Clinic were negative in five patients tested and serological tests for hepatitis B and C, antinuclear antigen, double stranded DNA, and cryoglobulins were uniformly negative. Blood and urine cultures were not done in any patients at the time of kidney biopsy. All patients had persistent hematuria and/or proteinuria following diagnosis of post-infectious glomerulonephritis on kidney biopsy (range, 4 months to 48 months; mean 14.9 months). Nine of the 11 patients were previously healthy prior to developing kidney disease, while one patient had hypertension and one had a history of pancreatitis. Of the 11 patients, two patients had family history of kidney disease.

Kidney Biopsy Findings (Table 2)

Kidney biopsies from all patients were interpreted at the renal pathology laboratory, Mayo Clinic, Rochester, MN. Three patients were biopsied twice in view of persistent hematuria

and proteinuria. All biopsies showed a proliferative glomerulonephritis. The most common pattern was a diffuse endocapillary proliferative glomerulonephritis (5 patients) followed by a mesangial proliferative (4 patients) and a membranoproliferative (1 patient) glomerulonephritis. One kidney biopsy showed a severe necrotizing and crescentic glomerulonephritis. IF microscopy showed bright (3+) mesangial and capillary wall C3 staining in all but one case (#11), which showed mild (1+) C3 staining. Two cases also showed mild mesangial and capillary wall staining for IgG (1–2+). There was no staining for immunoglobulins or C3 along the tubular basement membranes. EM showed the hallmark of post-infectious glomerulonephritis in all cases, i.e., hump-like subepithelial deposits, which were numerous in 6 patients. Ten of 11 patients also had mesangial and subendothelial deposits. Representative LM, IF and EM are shown in Figure 1.

Evaluation of the Alternative Pathway of Complement (Table 3)

Functional and genetic studies of the alternative pathway identified autoantibodies or mutations in complement genes in 10 of 11 patients. Seven patients were positive for C3Nefs, which were associated with other functional abnormalities of the AP in six patients. Four patients had mutations of complement genes including three patients with mutations in *CFH* and one patient with a mutation in *CFHR5*. The *CFH* mutations included a frameshift – c.2171delC, p.Thr724fsSTOP725 – and two missense variants – c.1699A>G,p.Arg567Gly and c.3350A>G,p.Asn1117Ser. The single missense variant in *CFHR5* was c.646-647AA>TT,p.Asn216Phe. None of the missense variants is reported in NHLBI Exome Sequencing Project, a database of over 10,000 chromosomes.

Treatment and Clinical Follow-up

Six of the 11 patients were treated with ACE inhibitors and angiotensin II blockers (renin-angiotensin system (RAS) blockade) in addition to corticosteroid therapy ranging from 4 weeks to 1 year. Two patients were treated conservatively with RAS blockade only and did not receive steroids or other forms of immunosuppressive therapy. One patient with crescents received cyclophosphamide followed by mycophenolate mofetil with stabilization of renal function. One patient was on dialysis within 4 months of presentation and one patient received no treatment.

Follow-up ranged from 4 to 48 months. In general, patients did well with no significant decline in renal function, both in the short and long term. On presentation, the mean serum creatinine and eGFR (excluding patient 5) were 1.96 mg/dL and 58 ml/min, respectively; follow-up means were 1.06 mg/dL and 72 ml/min (mean follow-up, 14.9 months). Only three patients had 24-hour urinary protein quantitation at last follow-up, which ranged from 900 mg to 7000 mg/24 hours (mean 3900 mg/24 hours). In three patients proteinuria was present but not quantified, and in four patients proteinuria data were not available (one patient was on dialysis). The patient who progressed to dialysis presented with a serum creatinine of 3.1 mg/dL. Repeat C3 levels normalized in four patients, while they remained low in three patients (follow-up from 1 year to 23 months).

DISCUSSION

Post-infectious glomerulonephritis is a relatively common glomerulonephritis that affects both children and adults.^{1, 8-10} Patients typically present with nephritic syndrome or acute renal failure, which rapidly resolve. In a minority of patients, however, hematuria and proteinuria persist or there is progression to end stage kidney disease.^{10, 14} The cause of persistent hematuria and proteinuria is not known. Kidney biopsy done in such cases shows features of post-infectious glomerulonephritis, i.e. proliferative glomerulonephritis on LM, bright glomerular C3 staining with or without immunoglobulins on IF, and subepithelial humps on EM. We also include cases of persistent hematuria and proteinuria that show features of post-infectious glomerulonephritis on kidney biopsy, but have no evidence of a preceding infection. We classify these patients as 'atypical' post-infectious glomerulonephritis and they form the basis of our study. Thus, patients with persistent hematuria and proteinuria, and kidney biopsy findings of a post-infectious glomerulonephritis, with or without a preceding infection, are included in the study. In this study, we show that such patients have an underlying abnormality of the AP of complement.

Most patients that are clinically diagnosed with post-infectious glomerulonephritis recover full renal function and are not biopsied, and hence as a group are difficult to study. However, persistent hematuria and proteinuria, in the setting of a prior clinical diagnosis of post-infectious glomerulonephritis, is an indication for kidney biopsy. We propose that when an infection occurs it triggers the AP, which under normal circumstances is quickly brought under control once the infection abates. However, in patients with a defect in AP regulation, there is continual AP activation with deposition of complement proteins and their breakdown products in the glomeruli, even after resolution of the infection, that leads to a development of 'atypical' proliferative glomerulonephritis. If the defect is mild, AP control occurs albeit at much slower rate than normal and in these patients, the glomerulonephritis eventually resolves. If the defect in AP regulation is more severe, hematuria and proteinuria persist, often exacerbated by recurrent bouts of infection (Fig 2). Thus, in 'atypical' post-infectious glomerulonephritis, an infection unmasks the underlying AP abnormality. In our study, we had documentation of infection in only five of 11 patients raising the possibility that sub-clinical infections may have occurred in the remaining patients. These are the cases that showed biopsy findings of post-infectious glomerulonephritis, yet had no clinical evidence of a preceding infection.

The role of AP activity in post-infectious glomerulonephritis is supported by other studies.¹⁵ As early as 1985, Meri and colleagues showed that sera from four patients with post-streptococcal glomerulonephritis contained factors other than immune-complexes that activated the complement system.¹⁶ Hisano et al., by immunohistochemical staining methods showed that glomeruli in post-infectious glomerulonephritis contained components of both the lectin and AP of complement.¹⁷ We have also completed laser microdissection and mass spectrometry of glomeruli of atypical post-infectious glomerulonephritis and verified the presence of AP complement proteins and their breakdown products in diseased glomeruli.¹⁸ Another indirect evidence of the role of AP is persistently low C3 levels noted in a small percentage of patients with post-infectious glomerulonephritis, even though C3 titers typically normalize within 8 weeks of resolution of the infection.^{19, 20}

In this study of ‘atypical’ post-infectious glomerulonephritis patients, we show that such patients have an underlying defect in the AP of complement. In 10 of the 11 patients, we demonstrated abnormalities in AP regulation. Five patients had C3Nefs detected by C3CSAP. C3Nefs are autoantibodies to C3 convertase that impair its control by protein regulators of complement activity, effectively prolonging the half-life of C3 convertase from a few seconds to 4–60 minutes.²¹ In two patients, IFE was positive. This assay does NOT detect antibodies but rather measures the presence of C3c in the serum as an indication of C3 convertase dysregulation. Four patients also had novel variants in complement-regulatory genes. *CFH*, which carried variants in three patients, is the most important fluid-phase regulator of the AP. It competes with factor B for binding to C3b to control formation of C3 convertase, promotes decay of formed C3 convertase, and serves as a cofactor for factor I to degrade C3b. We also detected a novel variant in *CFHR5*, a member of the factor H gene family, which is also a regulator of the C3 convertase. None of these variants is reported in NHLBI Exome Sequencing Project, a database of over 10,000 chromosomes, and current data suggest that rare variants such as those reported here make an important contribution to human phenotypic variation and disease susceptibility.²² Consistent with this possible functional effect, when we applied three commonly used algorithms (SIFT, PolyPhen2 and BLOSUM) to predict the consequence of the non-synonymous variants we identified, in each case at least two of these three programs classified these variants as damaging (predicted to have an effect on function).^{22–24} Our results are also supported by a case report showing persistent glomerulonephritis following streptococcal infection in a patient with *CFHR5* deficiency.²⁵ Nevertheless, functional testing of the isolated mutant proteins was not performed and therefore the pathological significance of these variants remains speculative.

Recent studies have shown that dysregulation of the AP also results in a proliferative glomerulonephritis called C3 glomerulonephritis (C3GN). C3GN is characterized by glomerular C3 deposition and the presence of numerous deposits in the mesangium and capillary walls, including subepithelial deposits.^{18, 26–29} Thus, there is considerable overlap in the biopsy findings of patients with ‘atypical’ post-infectious glomerulonephritis and C3GN.²⁶ This overlap is not surprising since both ‘atypical’ post-infectious glomerulonephritis and C3GN are due to abnormalities of AP of complement. However differences include the diffuse proliferative pattern of glomerulonephritis with ‘atypical’ post-infectious glomerulonephritis, as opposed to the membranoproliferative glomerulonephritis most commonly seen with C3GN, and the possible presence of Ig’s in ‘atypical’ post-infectious glomerulonephritis, which are typically absent in C3GN. On electron microscopy, ‘atypical’ post-infectious glomerulonephritis shows numerous subepithelial humps with mesangial and subendothelial deposits, while in C3GN there are numerous mesangial and subendothelial deposits and only occasional subepithelial deposits (Table 4). It should be pointed out that subepithelial humps can be present occasionally in Henoch-Schonlein purpura and Dense Deposit Disease.

Finally, we speculate that post-infectious and ‘atypical’ post-infectious glomerulonephritis are conceptually similar to hemolytic uremic syndrome (HUS) and atypical hemolytic uremic syndrome (aHUS) in that both HUS and post-infectious glomerulonephritis are

caused by an infection, while in aHUS and ‘atypical’ post-infectious glomerulonephritis, although there may be an infectious trigger, it is the underlying abnormality of the AP that drives the disease process.

To summarize, we define the entity of ‘atypical’ post-infectious glomerulonephritis that mimics post-infectious glomerulonephritis on kidney biopsy, yet behaves differently in that these patients have persistent proteinuria and hematuria and may progress to end stage kidney disease. We show that patients with ‘atypical’ post-infectious glomerulonephritis have an underlying abnormality in the AP of complement. Based on our data, we recommend testing for abnormalities in the AP of complement in all patients with ‘atypical’ post-infectious glomerulonephritis. Novel treatment strategies that target the underlying complement defect should also be considered in patients with progressive renal failure.

METHODS

Renal biopsies from 11 Mayo Clinic patients were evaluated. In all cases, routine work-up including light, immunofluorescence and electron microscopy was performed. Clinical information was obtained from the charts. The Institutional Review Boards at the Mayo Clinic and University of Iowa approved the study.

Functional Assays of Complement Activity

C3Nefs and factor H autoantibodies were detected, and the hemolytic assay, alternative pathway functional assay (APFA) and soluble membrane attack complex (sMAC) were completed, as previously described.^{18, 21} All functional assays were repeated three times.

Genetic Testing

Coding regions and intron-exon boundary junctions of *CFH* (MIM#134370; NM_000186), *CFHR5* (MIM#608593; NM_030787.3), *CFI* (MIM#217030; NM_000204.3), *CD46* (MIM#120920; NM_002389.3), *CFB* (MIM#138470; NM_001710.5) and *C3* (MIM#120700; NM_000064.2) were amplified and screened for mutations and polymorphisms using bi-directional sequencing as previously described.³⁰

Copy Number Variation

Multiplex-ligation probe amplification to detect deletion of *CFHR3-CFHR1* was completed as described.³¹

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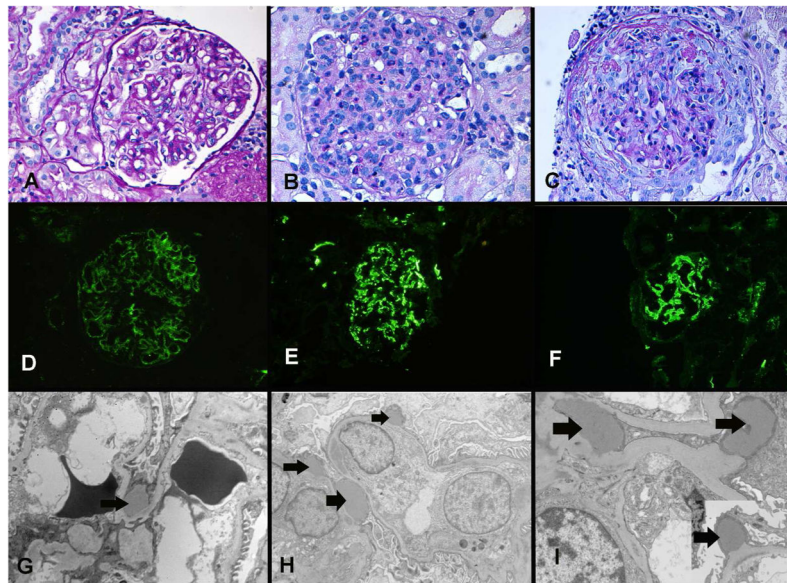


Figure 1. Representative light microscopy, immunofluorescence microscopy and electron microscopy from 3 patients are shown. Each column represents one case. Light microscopy: (A) Patient # 8 shows a mesangial proliferative glomerulonephritis, (B) Patient # 9 shows a diffuse proliferative glomerulonephritis, (C) Patient # 7 shows a crescentic glomerulonephritis. (D–F) Bright C3 staining in the mesangium and along capillary walls. (G–I) Subepithelial hump-like deposits (black arrows) in all 3 cases on electron microscopy. Figure 1-I also shows an insert with a classic subepithelial-hump in patient #7.

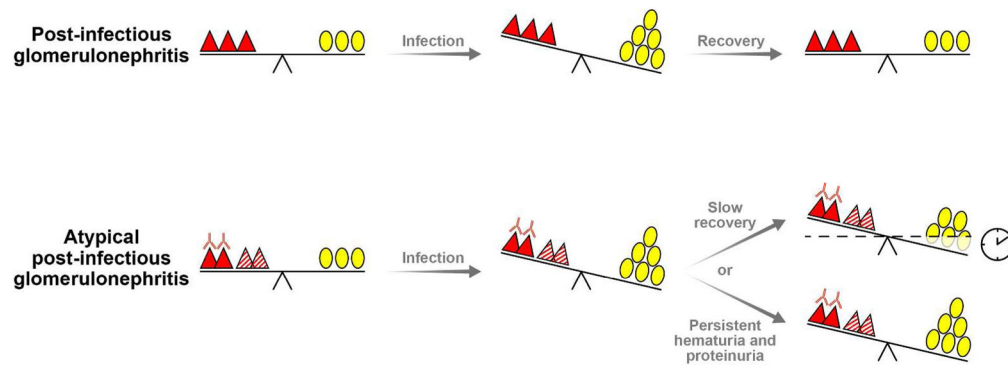


Figure 2.

Schematic representation of complement and ‘atypical’ post-infectious glomerulonephritis. Top panel shows normal balance of complement regulating proteins (red triangles) and complement factors (yellow oval structures). Following development of post-infectious glomerulonephritis, there is activation of the alternative pathway of complement represented by increase in complement factors. Following resolution of the infection, the complement cascade is quickly brought into control with restoration of balance. Lower panel showing atypical’ post-infectious glomerulonephritis due to the disruption of the complement cascade that results in a ‘persistent’ and ‘slowly resolving’ glomerulonephritis. Antibodies to complement regulating protein (inverted Y structures) or mutation/polymorphisms in complement regulating proteins (striped triangles) result in continual activation of the complement cascade following an infection. In case of ‘slowly resolving’ ‘atypical’ post-infectious glomerulonephritis the complement cascade is slowly brought under control, while in ‘persistent’ atypical post-infectious glomerulonephritis the complement cascade is continually activated, even after resolution of the infection.

Table 1

Clinical features and laboratory evaluation

Patient	Age/Sex At presentation	Serum Cr at presentation mg/dL	Urinalysis RBC/HPF	Urinary protein (mg/24hours)	C3/C4 mg/dL	Serum Creatinine at follow-up
1	71/F	1.7	41-50, <25% dRBC	614	46/24	0.78 (12 m)
2	52/F	1.44	50-100, > 25% dRBC	6389	76/26**	1.1 (15 m)
3	14/M	1.3	21-30, >25% dRBC	15760	19/13	1.3 (30 m)
4	60/M	1.1	50-100, >25% dRBC	874	57/35	1.4 (48 m)
5	47/F	3.1	21-30, No report on dRBC	204 while on dialysis	56/47	on dialysis 4m after presentation
6	22/M	2.02	50-100 No report on dRBC	10390	12/normal	1.6 (4 m)
7	22/M	1.8	50-100 No report dRBC	800	135/37	1.2 (6 m)
8	17/F	0.7	Hematuria UA report*	1156	115/20	0.7 (12 m)
9	2.5/M	0.5	50-100, >25% dRBC	3+, not quantitated	81/23	0.4 (recent patient, 4 m)
10	20/M	1.32	31-40, <25% dRBC	12400	3/normal	1.65 (8 m)
11	61/F	0.8	31-40, <25% dRBC	507	108/33	0.5 (10 m)

dRBC= dysmorphic RBC, C3 normal range (75-175 mg/dL), C4 normal range (14-40 mg/dL), m=month, yr= year,

* UA at presentation not available, low or normal C3/C4 as per notes or laboratory results- values not given

** C3 levels at outside laboratory at presentation had normal range listed as 90-150 md/dL

Table 2

Kidney biopsy findings

Patient	Pattern of Injury, Globally sclerosed/total glomeruli	Tubulo-interstitial Scarring	Immunofluorescence Microscopy (CW and mesangial)	Electron Microscopy Deposits
1	Mesangial Proliferative glomerulonephritis, 2/10	25	C3 (2+)	SU, SE, MES
2	Diffuse endocapillary proliferative, 4/23	25	C3+, IgG (1+)	SU, IN, MES
3	Diffuse endocapillary proliferative, 2/29	10	C3 (3+), IgG (2+) IgM, lambda, kappa (1+)	SU, SE, MES
4**	Mesangial proliferative, 0/18	10	C3 (3+), IgM (2+)	SU, SE, IN, MES
5	Diffuse endocapillary proliferative and exudative, 3/10	20	C3 (3+)	SU
6	Membranoproliferative with crescents, 2/9	5	C3 (3+), IgM (trace)	SU, SE, IN, MES
7	Necrotizing and crescentic, 1/20	5	C3 (3+)	SU, MES
8	Mesangial proliferative, 4/11	30	C3 (2-3+)	SU, SE, IN, MES
9	Diffuse endocapillary proliferative and exudative with crescents, 0/40	0	C3 (3+)	SU, SE, IN, MES
10**	Diffuse endocapillary proliferative, 0/30	0	C3 (3+)	SU, SE, IN, MES
11**	Mesangial proliferative, 3/14	10	C3 (1+)	SU, SE, IN, MES

* SE- subendothelial, SU- subepithelial, IN- intramembranous, MES- mesangial, CW-capillary wall, GS-globally sclerosed.

** Biopsied twice

Table 3

Complement abnormalities.

Patient	CFH	CFHK5	FH Antibodies ¹	Hemolytic Assay ²	APFA ³	C3NeF	sMAC ⁴
1	c.2171delC, p.Thr724fsX 725	No mutations	Negative	ND	ND	Negative	0.24 mg/L
2	No mutations	c.646–647 AA>TT, p.Asn216Phe	Negative	0% Normal	63% abnormal	Negative	0.21 mg/L
3	No mutations	No mutations	Negative	1% Normal	63% abnormal	Positive (C3CSAP ⁵)	ND
4	No mutations	No mutations	Negative	0% Normal	1% abnormal	Positive (IFE ⁶)	1.23 mg/L
5	No mutations	No mutations	Negative	12% Abnormal	34% abnormal	Positive (IFE)	0.48 mg/L
6	No mutations	No mutations	Negative	0% Normal	14% abnormal	Positive (both assays)	ND
7	c.3350A>G, p.Asn1117Ser	No mutations	Negative	0% Normal	80%	Negative	ND
8	No mutations	No mutations	Negative	0% Normal	123%	Negative	0.13 mg/L
9	No mutations	No mutations	Negative	9% Abnormal	77%	Positive (both assays)	ND
10	c.1699A>G, p.Arg567Gly	No mutations	Negative	0% Normal	0% abnormal	Positive (both assays)	2.03 mg/L
11	No mutations	No mutations	Negative	0% normal	130%	Positive (C3CSAP)	0.21 mg/L

¹ normal titer <1:50;² normal <3%³ normal 65%–130%;⁴ normal <0.3 mg/L;⁵ C3CSAP, C3 convertase stabilizing assay with properdin;⁶ immunofixation electrophoresis,

APFA-alternative pathway functional assay

Table 4

Kidney Biopsy features of post-infectious glomerulonephritis, 'atypical' post-infectious glomerulonephritis, and C3 glomerulonephritis.

	Post-infectious Glomerulonephritis (PIGN)	'Atypical' Post-infectious Glomerulonephritis (aPIGN)	C3 glomerulonephritis (C3GN)
LM	Diffuse proliferative, less commonly mesangial proliferative or crescentic	Diffuse proliferative, less commonly mesangial proliferative or crescentic	Membranoproliferative, less commonly mesangial proliferative
IF	Bright mesangial and capillary wall C3, usually with Ig's (garland pattern)	Bright mesangial and capillary wall C3, usually without Ig's. If present IgG (trace to 1+)	Bright mesangial and capillary wall C3, usually without Ig's
EM	Numerous subepithelial humps, few mesangial and subendothelial deposits	Numerous subepithelial humps, many mesangial and subendothelial deposits, ± intramembranous deposits	Many mesangial and subendothelial deposits, ± few intramembranous and subepithelial humps

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