Atypical postinfectious glomerulonephritis is associated with abnormalities in the alternative pathway of complement

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Postinfectious 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 postinfectious glomerulonephritis even in the absence of any evidence of a preceding infection. The cause of such 'atypical' postinfectious glomerulonephritis, with or without evidence of preceding infection, is unknown. Here we show that most patients diagnosed with this 'atypical' postinfectious 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' postinfectious glomerulonephritis.

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Postinfectious glomerulonephritis is a type of glomerulonephritis seen in both children and adults after an infection. The glomerulonephritis is manifested by the 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 postinfectious glomerulonephritis is thought to be due to (1) glomerular *in situ* deposition of bacterial antigens with subsequent antibody buildup and formation of *in situ* immune complexes and/or (2) glomerular deposition of circulating immune complexes.[2–6]

The characteristic features of postinfectious 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 postinfectious glomerulonephritis is made on the basis of 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 after postinfectious 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' postinfectious glomerulonephritis have been used to describe these entities.

During an infection that triggers the development of postinfectious glomerulonephritis, there is activation of the alternative pathway (AP) of complement.[4,11,12] After elimination of the infection, immune complexes are cleared, the 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 downregulation after 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' postinfectious 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 postinfectious glomerulonephritis on kidney biopsy to determine whether an underlying abnormality of the AP of complement could be identified. The study included six cases with a kidney biopsy diagnosis of postinfectious 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' postinfectious glomerulonephritis. The diagnostic criteria of 'atypical' postinfectious glomerulonephritis were as follows: (1) persistent hematuria and proteinuria, with or without a history of preceding infection; (2) renal biopsy showing features of postinfectious 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; and (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 when there was persistent hematuria and proteinuria. In 5 of the 11 patients, there was a history of upper respiratory tract infection, whereas 1 patient (patient no. 9) had an upper respiratory infection and impetigo. In the remaining six patients, it was not clear from the outside records whether there had been an antecedent illness. The upper respiratory illnesses varied from 4 days to 1 month before the development of kidney disease. Time from the development of kidney disease to kidney biopsy varied from 2 weeks to 15 months (mean 4.1 months), although in one case (patient no. 3) the biopsy was performed 1 day after the development of kidney disease. There were 5 female and 6 male patients (age range, 2–71 years; mean, 35.1 years), including 1 child, 2 teenagers, and 8 adults. The serum creatinine level at presentation ranged from 0.5 to 3.1 mg/dl (mean, 1.4 mg/dl), with an estimated glomerular filtration rate of 16–109 ml/min (mean 58 ml/min per 1.73 m^2). The serum creatinine at the 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 h (mean, 5139 mg/24 h). C3 levels were low in seven patients, with a range of 3–135 mg/dl (mean, 64.3 mg/dl; normal range 80–175 mg/dl), whereas it was within normal levels in four patients. C4 levels were normal in all patients. Platelet counts were low in patient no. 1, whereas they were normal in all other patients. Schistocytes were absent on the peripheral smear in patient no. 1. Hemoglobin levels ranged from 7.9 to 14.3 g/dl (mean 11.1 g/dl). Anti-streptolysin O 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 performed in any patients at the time of kidney biopsy. All patients had persistent hematuria and/or proteinuria following diagnosis of postinfectious glomerulonephritis on kidney biopsy (range, 4–48 months; mean, 14.9 months). Nine of the eleven patients were previously healthy before developing kidney disease, whereas one patient had hypertension and one had a history of pancreatitis. Of the 11 patients, two patients had a family history of kidney disease.

Table 1 | Clinical features and laboratory evaluation

Patient	Age/sex at presentation	Serum creatinine at presentation mg/dl	Urinalysis RBC/HPF	Urinary protein (mg/24 h)	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	1.4	50–100, > 25% dRBC	6389	76/26[a]	1.1 (15 m)
3	14/M	1.3	21–30, >25% dRBC	15,760	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, 4 m after presentation
6	22/M	2.0	50–100, No report on dRBC	10,390	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[b]	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	1.3	31–40, <25% dRBC	12,400	3/Normal	1.65 (8 m)
11	61/F	0.8	31–40, <25% dRBC	507	108/33	0.5 (10 m)

Abbreviations: C3, normal range 75–175 mg/dl; C4, normal range 14-40 mg/dl; dRBC, dysmorphic RBC; HPF, high power field; RBC, red blood cell; m, month; UA, urinalysis.
[a]C3 levels at outside laboratory at presentation had normal range listed as 90–150 mg/dl.
[b]UA presentation not available, low or normal C3/C4 as per notes or laboratory result values not given.