

# Post-infectious Proliferative Glomerulonephritis with Monoclonal Immunoglobulin G Deposits Associated with Complement Factor H Mutation

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## Abstract

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A 55-year-old man developed rapidly progressive glomerulonephritis and nephrotic syndrome. A kidney biopsy specimen showed diffuse proliferative and crescentic glomerulonephritis with monoclonal IgG1 $\kappa$  humps, and nephritis-associated plasmin receptor, indicating infection-associated proliferative glomerulonephritis with monoclonal immunoglobulin G deposits (PGNMID). Despite dialysis-dependent renal failure, symptomatic therapy resulted in spontaneous recovery of the renal function, mimicking post-infectious glomerulonephritis (PIGN). A heterozygous complement factor H mutation was detected by comprehensive genetic testing of alternative pathway regulatory genes, which might lead to persistent infection-triggered alternative pathway activation and account for severe glomerulonephritis. Post-infectious PGNMID and PIGN might share common clinical presentations and pathogenesis related to the complement pathway.

**Key words:** alternative pathway, complement, glomerulonephritis, infection, monoclonal immunoglobulin

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## Introduction

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Proliferative glomerulonephritis with monoclonal immunoglobulin G (IgG) deposits (PGNMID) is a recently described entity characterized by monoclonal IgG deposits. In the decade since the first reported case (1), PGNMID has been reported increasingly often because of the broader availability of staining for light-chain isotypes and  $\gamma$  heavy-chain subclasses (2-5). However, the pathophysiology of PGNMID with heterogeneous morphology and renal survival is not fully understood. Efficient therapeutic approaches are still not established for individuals with progressive PGNMID, eventually leading to end-stage renal disease (ESRD). In contrast, patients with recovery of the renal function or remission of proteinuria with renin-angiotensin system (RAS) blockade alone (1, 2) or following resolution of a preceding infection have been reported (6). This report describes a patient with infection-associated PGNMID and a

mutation of complement factor H (*CFH*). The patient showed spontaneous partial recovery of the renal function, mimicking post-infectious glomerulonephritis (PIGN), despite diffuse proliferative and circumferential crescentic glomerulonephritis with dialysis-dependent renal failure.

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## Case Report

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A 55-year-old Japanese man was referred and admitted to our hospital with rapidly progressive glomerulonephritis (RPGN) and nephrotic syndrome in December 2012. His serum creatinine (SCr) level was 0.63 mg/dL in 2011 (Table). Seven weeks earlier, he had been admitted to another hospital with hemorrhagic gastric ulcer and renal failure [SCr, 3.50 mg/dL; serum albumin, 2.7 g/dL; urine protein to creatinine ratio (UPCR), 12.3 g/gCr; and moderate hematuria] (Table), which gradually worsened until the referral. His medical history included obsolete tuberculosis, hypertension, and an emergent operation for perforated peptic ulcer at the

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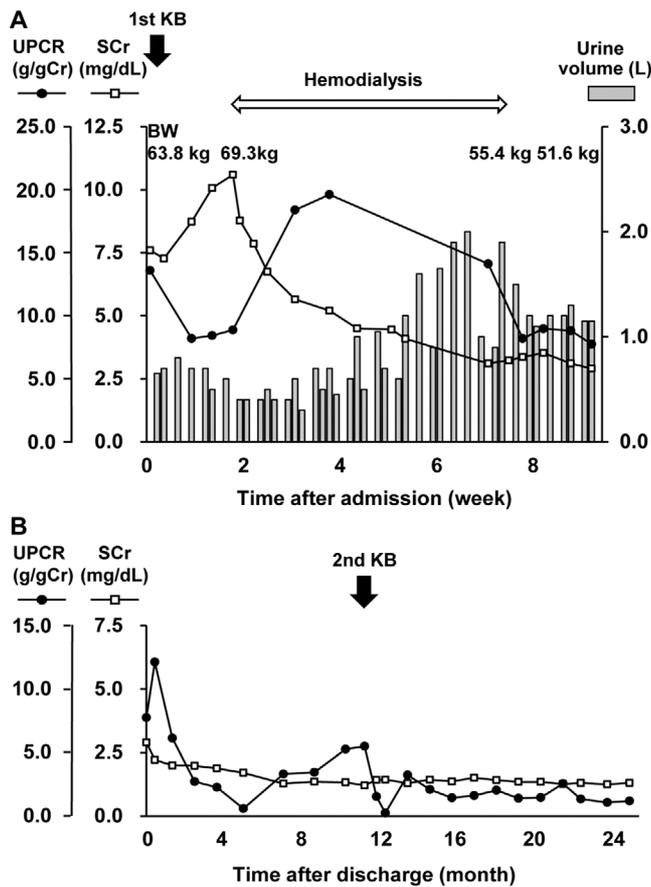
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**Table. Laboratory Findings of the Patient.**

|                                     | Before presentation | At presentation to another hospital | At first kidney biopsy | At second kidney biopsy |
|-------------------------------------|---------------------|-------------------------------------|------------------------|-------------------------|
| Total protein, g/dL                 | 7.2                 | 4.9                                 | 5.5                    | 6.2                     |
| Albumin, g/dL                       | 4.2                 | 2.7                                 | 1.7                    | 3.2                     |
| Urea nitrogen, mg/dL                | 13.4                | 62.5                                | 45.5                   | 17.9                    |
| Creatinine, mg/dL                   | 0.63                | 3.50                                | 7.60                   | 1.21                    |
| eGFR, mL/min/1.73 m <sup>2</sup>    | 102.4               | 15.6                                | 6.7                    | 49.6                    |
| UPCR, g/gCr                         | N/A                 | 12.3                                | 13.6                   | 5.49                    |
| C3, mg/dL (reference range, 65-135) | N/A                 | N/A                                 | 108                    | 97                      |
| C4, mg/dL (reference range, 13-35)  | N/A                 | N/A                                 | 43                     | 28                      |
| CH50, U/mL (reference range, 30-50) | N/A                 | 36.9                                | 61.6                   | 47.7*                   |

eGFR: estimated glomerular filtration rate, N/A: not applicable, UPCR: urine protein-to-creatinine ratio

\*Measured three months prior to the second kidney biopsy.



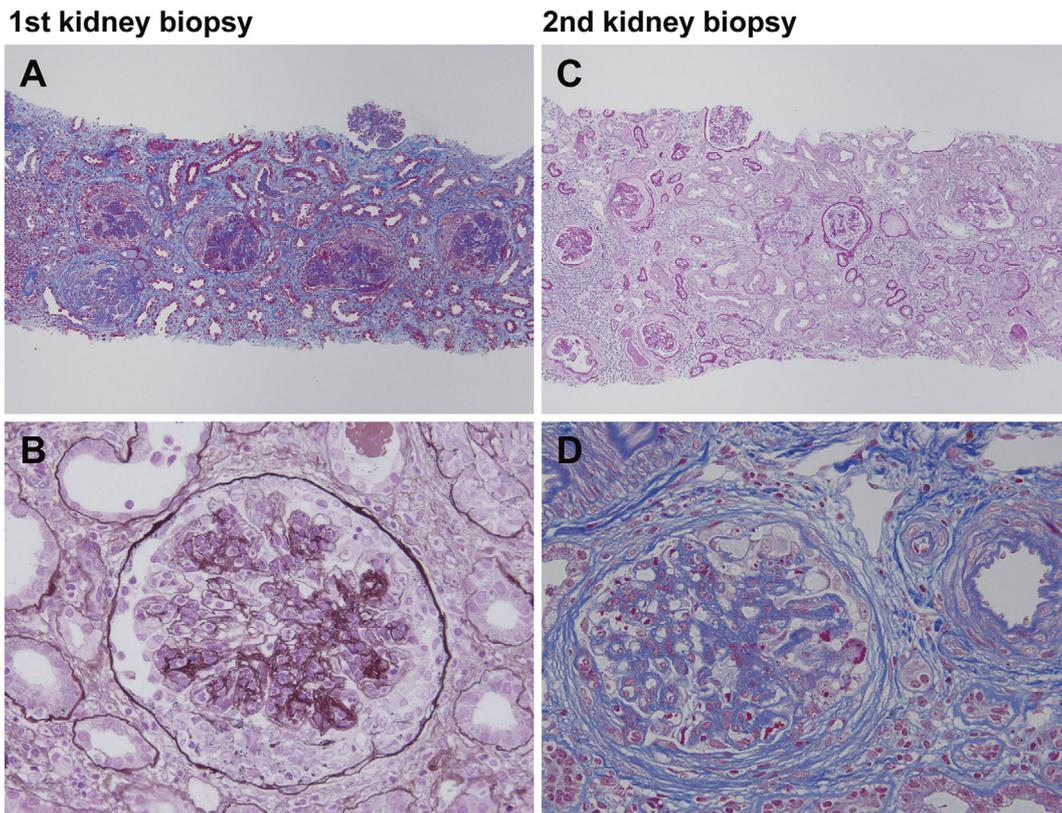
**Figure 1. Clinical course of the patient. Changes in the serum creatinine (SCr, continuous lines), urine protein-to-creatinine ratio (UPCR, dotted lines), and urine volume during hospitalization (A) and after discharge (B). A: The first kidney biopsy (KB) was performed on hospital day 2. Hemodialysis was initiated on hospital day 13 due to oliguria and congestion, and symptomatic therapy resulted in a gradual decrease in the SCr and increase in the urine volume, and hemodialysis was ceased on day 52. B: The second KB was performed due to transient recurrence of nephrotic-range proteinuria. BW: body weight, KB: kidney biopsy, UPCR: urine protein to creatinine ratio, SCr: serum creatinine**

height, and blood pressure were 64.1 kg, 174 cm, and 169/105 mmHg, respectively, and he was afebrile. The laboratory findings (Table) were as follows: hemoglobin, 9.6 g/dL; white blood cell count, 9,020/ $\mu$ L; platelet count,  $46.2 \times 10^4$ / $\mu$ L; serum total protein, 5.5 g/dL; albumin, 1.7 g/dL, total cholesterol, 166 mg/dL, creatinine, 7.60 mg/dL; sodium, 144 mEq/L; potassium, 3.4 mEq/L; chloride, 110 mEq/L; C-reactive protein, 0.14 mg/dL; IgG, 1,330 mg/dL; IgA, 136 mg/dL; IgM, 82 mg/dL;  $\kappa$ -light chain, 179.0 mg/L (normal range, 2.42-18.92);  $\lambda$ -light chain, 78.40 mg/L (normal range, 4.44-26.18);  $\kappa/\lambda$  ratio, 2.283 (normal range, 0.248-1.804). A urinalysis revealed heavy hematuria with proteinuria at 13.6 g/gCr and a variety of casts. Anti-streptolysin O and anti-streptokinase antibodies were not elevated. Anti-nuclear and anti-neutrophil cytoplasmic antibodies as well as HBcAb, HBsAg, and serum cryoglobulins were negative. Serum or urine paraproteins were not detected by immunofixation electrophoresis. Chest X-ray showed bilateral pleural effusions, and echocardiography showed no vegetations.

The first kidney biopsy was performed on hospital day 2 (Fig. 1). Light microscopy showed 35 glomeruli, including one glomerulus with global sclerosis. Numerous circumferential cellular crescents and diffuse endocapillary and mesangial proliferation with double contour formation along the capillary walls were observed (Fig. 2A and B). Immunofluorescence showed granular IgG, IgG1,  $\kappa$  light chain, and C3 deposits predominantly along the capillary walls, with undetectable IgM, IgA, C1q, IgG2-4, and  $\lambda$  light chain (Fig. 3A-H). Electron microscopy (EM) showed subepithelial and subendothelial deposits, including hump-like shaped deposits (Fig. 4A and B). Positive immunofluorescent staining for nephritis-associated plasmin receptor (NAP1r) and positive *in situ* zymography for plasmin (Fig. 5A and B) suggested a preceding infection as the etiology of glomerulonephritis (7), which could partially explain the spontaneous recovery of the renal function later observed in this case, similar to that observed in PIGN.

PIGN usually involves activation of the complement pathway, especially the alternative pathway (AP) (8, 9), and previous reports have shown persistent and irreversible renal impairment in PIGN cases with defects in the AP (10, 11). Thus, a comprehensive genetic study was performed using

ages of 31, 53, and 54, respectively. There was no family history of kidney disease. On admission, his body weight,



**Figure 2.** Representative light microscopy. **A:** Diffuse proliferative and circumferential crescentic glomerulonephritis at the first kidney biopsy (Masson trichrome,  $\times 40$ ). **B:** Mesangial and endocapillary proliferation with double contours along the capillary walls and a cellular crescent [periodic acid-methenamine-silver (PAM) stain,  $\times 200$ ]. **C:** Increased global sclerosis with moderate tubular fibrosis at the second kidney biopsy (periodic acid-Schiff stain,  $\times 40$ ). **D:** A glomerulus showing a fibular crescent and mesangial proliferation with double contours along the capillary walls (Masson trichrome,  $\times 400$ ).

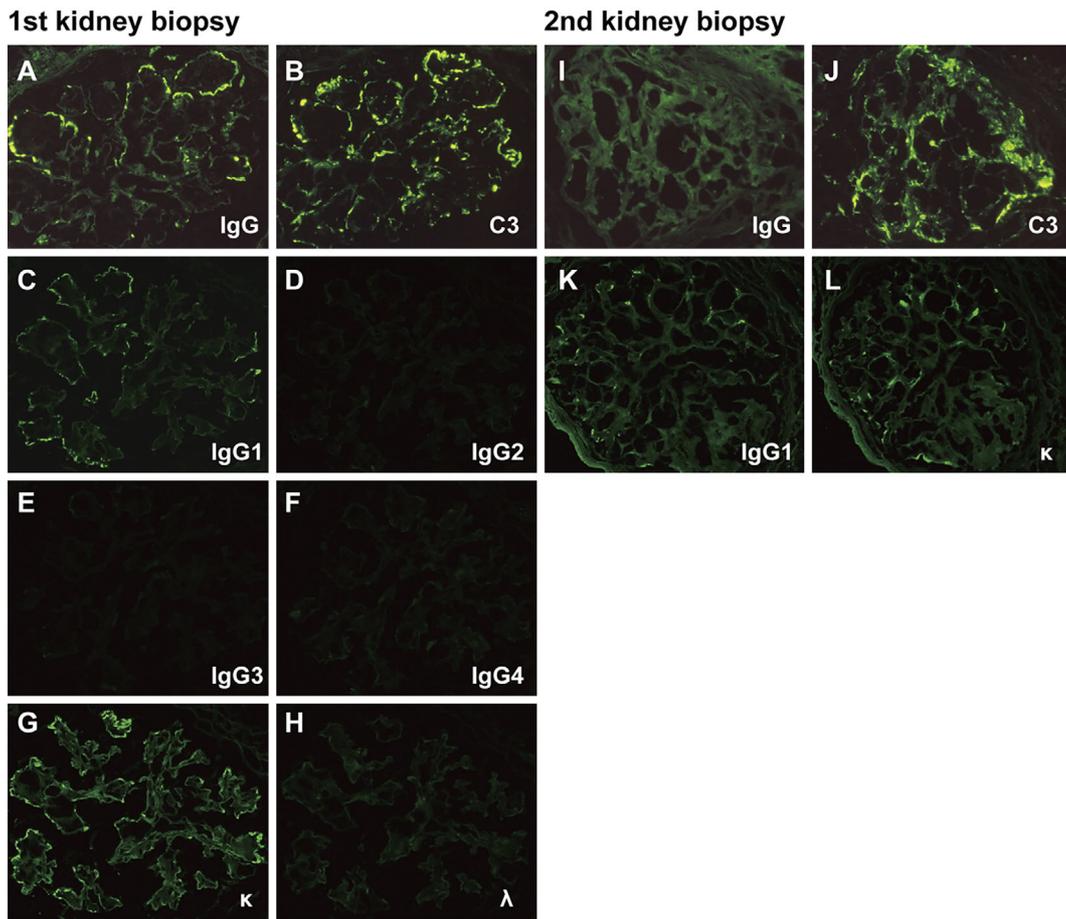
the patient's blood sample to investigate potential mutations of AP regulatory genes, including *C3*, *CFH*, *CFHR1*, *CFHR3*, *CFHR5*, *CFI*, *CFB*, and *CD46*, which revealed a heterozygous missense variant, c.2392G>A, p.D798N in *CFH*. The patient provided his written informed consent, and the detailed methods are described in greater detail elsewhere (12). This mutation is a very rare variant (rs55931547) with the allele frequency being 0.00003307 in ExAC (<http://exac.broadinstitute.org/>), and no published functional data are available given the novel variant in relation to the disease. However, according to the CADD database (<http://cadd.gs.washington.edu/>), which is the *in silico* protein function prediction program, the score is 12.4 ( $>10$ ), suggesting that this variant may cause the dysfunction of *CFH*.

Symptomatic therapy with no corticosteroids or immunosuppressants was started due to the repeated hemorrhagic ulcer and ameliorated decline in the renal function. On day 13 after admission, hemodialysis was initiated due to oliguria and congestion despite high-dose intravenous diuretics (Fig. 1). However, a gradual decrease in SCr with an increase in urine volume was observed two weeks after hemodialysis initiation, resulting in cessation of hemodialysis on

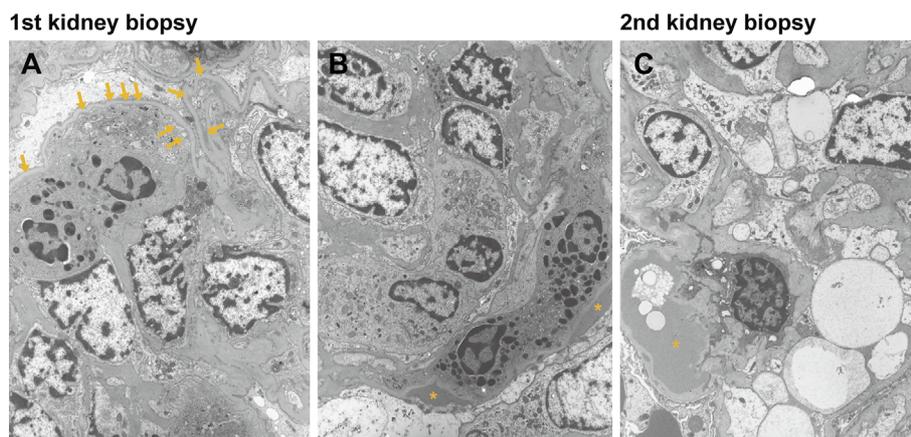
day 52. After discharge on hospital day 66, SCr and urinary protein decreased to 1.2 mg/dL and  $<1$  g/gCr, respectively. One year after discharge, the patient developed nephrotic-range proteinuria (Table). A second kidney biopsy performed at that time showed markedly increased sclerotic or collapsing glomeruli (approximately 70% of all glomeruli) with fibrous crescents (15-20%), moderate tubular atrophy, and fibrosis (Fig. 2C). The remaining glomeruli showed mesangial proliferation with double contour formation along the capillary walls (Fig. 2D). Predominant C3 deposits with weak deposits of IgG1 and  $\kappa$  light chain and subendothelial deposits were observed (Fig. 3I-L, 4C); however, NAP1r and plasmin deposits were absent (Fig. 5I and J). Nephrotic-range proteinuria spontaneously resolved, and the UPCr and SCr levels were within the ranges of 1-2 g/gCr and 1.2-1.5 mg/dL, respectively, for one year following discharge. Repeated serum and urine electrophoresis showed no paraproteins (Fig. 6).

## Discussion

This report described a patient with infection-associated PGNMID and a *CFH* mutation who developed RPGN,



**Figure 3.** Immunofluorescence study. (A-H) Immunofluorescence staining for C3 and IgG subtypes showing monoclonal IgG1κ predominantly along the capillary walls at the first kidney biopsy. A: IgG (+), B: C3 (++) , C: IgG1 (+), D: IgG2 (-), E: IgG3 (-), F: IgG4 (-), G: κ (+), and H: λ (-). (I-L) Immunofluorescence staining for IgG subtypes showing weak monoclonal IgG1κ deposition at the second kidney biopsy. I: IgG (+), J: C3 (++) , K: IgG1 (+), and L: κ (+).



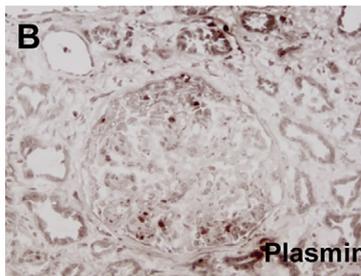
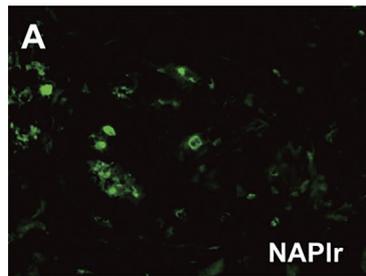
**Figure 4.** Electron microscopy. A: Electron-dense deposits (arrows) are predominantly seen in the subendothelium at the first kidney biopsy (×4,000). B: Subepithelial hump-shaped deposits (\*). C: Electron microscopy showing subendothelial deposits at the second kidney biopsy (\*, ×4,000).

nephrotic syndrome, and diffuse proliferative and crescentic glomerulonephritis. Symptomatic therapy led to spontaneous partial recovery of the renal function and remission of nephrotic syndrome, mimicking the clinical presentation of

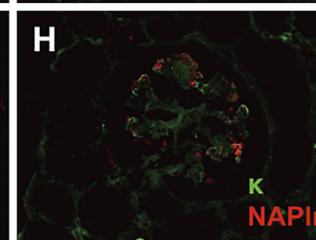
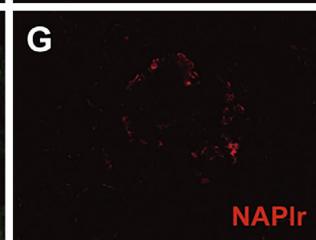
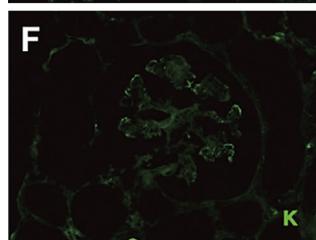
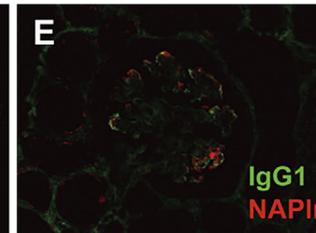
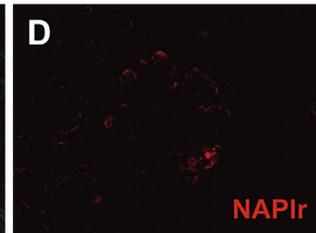
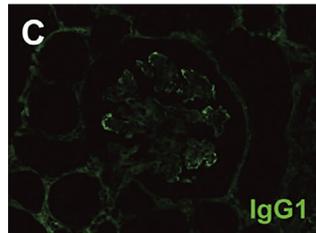
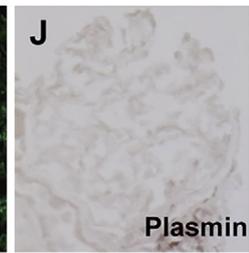
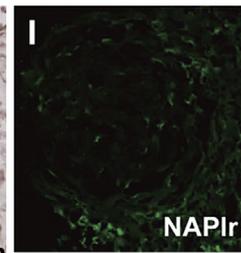
PIGN. Post-infectious PGNMID and PIGN may share common clinical presentations and pathogenesis.

In the largest case series of PGNMID (2), the predominant histology was membranoproliferative glomerulonephri-

## 1st kidney biopsy



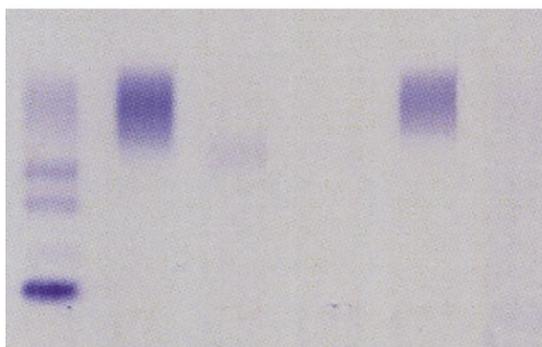
## 2nd kidney biopsy



**Figure 5.** Glomerular staining for nephritis-associated plasmin receptor (NAPIr) and plasmin activity. A: NAPIr staining labeled with fluorescein isothiocyanate (green) at the first kidney biopsy. B: Plasmin activity by *in situ* zymography with localization similar to NAPIr staining. (C-H) Representative photomicrographs of double immunofluorescence staining for IgG1 or  $\kappa$  (FITC; green) and NAPIr (Alexa Fluor 594; red). The distributions of IgG1 or  $\kappa$  (C or F) and NAPIr (D or G) were different in the merged images (E or H). I: Staining for NAPIr was negative at the second kidney biopsy. J: Plasmin was also negative.

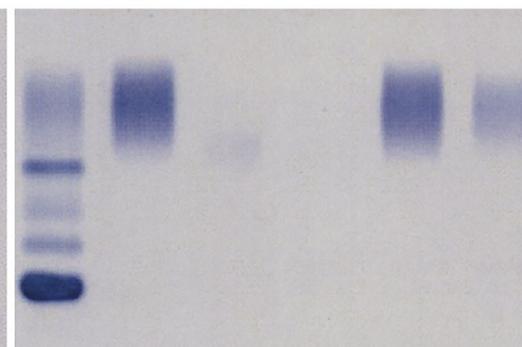
## Serum

SPE IgG IgA IgM  $\kappa$   $\lambda$



## Urine

SPE IgG IgA IgM  $\kappa$   $\lambda$



**Figure 6.** Serum and urine protein electrophoresis with immunofixation. Both serum (left) and urine (right) protein electrophoresis showed no bands within the IgG, IgA, IgM,  $\kappa$ , or  $\lambda$  columns.

tis (MPGN) (57%) and IgG3 $\kappa$  deposits (53%), followed by IgG1 $\kappa$  (22%); crescents were present in 32% of the cases. The morphology in our case was compatible with that of PGNMID and was different from that of a similar disease entity, monoclonal immunoglobulin deposition disease (MIDD), particularly light- and heavy-chain deposition disease (LHCDD): morphologically characterized by nodular

glomerulosclerosis by light microscopy, linear staining of both glomerular basement membranes and tubular basement membranes for a single heavy chain and a single light chain by immunofluorescence, and continuous linear deposition of granular electron-dense deposits inside glomerular basement membranes by electron microscopy (2). Serum or urine paraproteins were not detected, indicating that multiple

myeloma associated with glomerulonephritis was unlikely, although bone marrow biopsy was not performed. Lymphoma was also unlikely, based on a careful physical examination and CT scans. In addition, this case showed humps by EM and reversal from ESRD with symptomatic therapy, similar to that expected in patients with PIGN. Although the signs of overt infection were absent at the time of referral, positivity for NAPlr and plasmin indicated that a preceding infection was involved in the development of PGNMID and might account for the parallels between PIGN and post-infectious PGNMID cases.

NAPlr is a nephritogenic antigen originally isolated from group A streptococcus (GAS) with high homology in nucleotide and amino acid sequences to plasmin receptor. Glomerular deposition of NAPlr is usually seen in the early phase of acute poststreptococcal glomerulonephritis and pathogenically causes glomerular damage by trapping plasmin and maintaining its activity (7). However, NAPlr deposition is observed in other glomerular diseases as well, such as dense deposit disease or MPGN after streptococcal infection (13), and even after other bacterial infections such as pneumococcal infection (14) or staphylococcal infection (unpublished data). NAPlr is basically identical to streptococcal glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (7). The C-terminal sequences of NAPlr (streptococcal GAPDH), which are highly associated with plasminogen- and plasmin-binding activity, are completely identical to those of pneumococcal GAPDH (15). Therefore, GAPDH of multiple bacterial pathogens may share pathogenic roles with NAPlr in the development of glomerulonephritis. Neither the organism nor the site of infection could be determined in this case despite thorough physical examinations and work-ups. However, the lack of elevated anti-streptolysin O and anti-streptokinase antibodies suggested that an organism other than GAS with its NAPlr-like GAPDH likely caused glomerulonephritis in this case.

NAPlr is also known to convert C3 to C3b *in vitro*, indicating the direct involvement of NAPlr in activation of the complement pathway (16). Of note is that the glomerular distribution of NAPlr is basically different from that of IgG or C3 in acute poststreptococcal glomerulonephritis as well as other NAPlr-related glomerulopathy cases (13). C3 and/or IgG deposits are typically seen at subepithelial sites, whereas NAPlr is located in the inner side of the glomerular tufts. One possible explanation for this is that the direct complement activation by NAPlr is mediated predominantly in the circulation rather than *in situ* (13). Thus, the lack of any co-localization of NAPlr and IgG1 or  $\kappa$  in this case (Fig. 5C-H) was compatible with the findings from previous reports.

Activation of the complement pathway, predominantly AP, plays a pivotal role in PIGN, particularly in acute poststreptococcal glomerulonephritis (8, 9). Recent studies have shown that AP dysregulation can result in persistent and irreversible renal impairment in PIGN. Vernon et al. (10) reported a patient with a heterozygous mutation of CFHR5

that encodes CFH-related protein 5 presenting with persistent renal disease following streptococcal infection. More recently, Sethi et al. (11) reported 11 similar patients with atypical PIGN, defined as typical PIGN morphology accompanied by persistent proteinuria or hematuria. The authors suggested that infection-triggered AP activation was reversible in typical PIGN, whereas an underlying defect in AP resulting from genetic mutations of or autoantibodies to AP-regulatory proteins resulted in prolonged AP activation as well as severe and persistent glomerulonephritis.

In this patient, genetic testing revealed a heterozygous mutation of *CFH*, a primary regulator of AP. The *in silico* protein function prediction program CADD database suggested that this variant might cause dysfunction of *CFH*. *CFH* consists of 20 short consensus repeats (SCRs), and the variant detected in this patient was located in SCR 13. Previous studies have shown associations between *CFH* mutations and the development of various glomerular diseases, including atypical hemolytic uremic syndrome, MPGN, and dense deposit disease (17-19). The reported mutations were widely distributed over SCRs, including non-regulatory and non-recognition SCRs, 5-6 and 8-17 (19). *CFH* variants were also found in 3 of 11 patients with atypical PIGN (11). We therefore speculate that the underlying defect in AP resulting from the mutation-related *CFH* dysfunction was attributable to severe renal failure with incomplete recovery in this case, although definitive findings such as C3 nephritic factor suggesting AP dysregulation were not available. The reappearance of nephrotic-range proteinuria at the second kidney biopsy may be also due to an unapparent infection that triggered the reactivation of AP but was transiently resolved, presumably because of sufficient renoprotective treatment, including blood pressure control with an angiotensin-converting enzyme inhibitor and diuretics or lipid-lowering therapy as well as the low number of remaining glomeruli to be further affected. Post-infectious PGNMID and PIGN might share a common pathogenesis associated with AP activation.

Two similar cases of post-infectious PGNMID with spontaneous recovery after resolution of parvovirus B19 infection were recently reported (6). The authors speculated a mechanism in which parvovirus B19 infection triggered an immune reaction leading to proliferation of specific B-cell clones that produced monoclonal IgGs (6). Several case reports have shown recurrence of PGNMID after renal transplantation (20, 21), indicating that the recurrence was likely based on persistent circulating paraproteins in typical PGNMID (21). In contrast, infection-induced monoclonal IgG production and glomerular deposition is transient and is resolved by eradication of the infection in post-infectious PGNMID (6). Our patient also showed markedly weakened IgG and IgG1 $\kappa$  deposits at the second kidney biopsy. Post-infectious PGNMID may have an improved renal outcome compared with typical PGNMID, similar to that of PIGN, if the underlying AP dysregulation is absent. Thus, to avoid unnecessary immunosuppressive treatment, it is essential to

clarify the involvement of a preceding infection by examination for NAPlr or plasmin deposition in PGNMID patients.

In conclusion, this report describes a patient with post-infectious PGNMID and a *CFH* mutation that exhibited spontaneous partial recovery of the renal function. Post-infectious PGNMID may share a common clinical presentation and AP-related pathogenesis with PIGN.

**The authors state that they have no Conflict of Interest (COI).**

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