

Glomerulonephritis With Isolated C3 Deposits as a Manifestation of Subtotal Factor I Deficiency



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INTRODUCTION

The complement system is an essential effector of innate immunity that plays a crucial role in the defense against common pathogens and in host homeostasis.¹ Therefore, patients with complete complement deficiencies frequently present with recurrent bacterial infections or autoimmune diseases. At opposite, overactive or deregulated complement typically results in kidney diseases.^{S1} Atypical hemolytic uremic syndrome (HUS) and glomerulonephritis with isolated C3 deposits (C3GN) are 2 prototypes of complement-mediated kidney diseases due to deregulation of the alternative complement pathway (CAP).^{2,3,S2} C3GN is driven by autoantibodies that target the C3 or C5 convertases and less frequently by pathogenic variants in the genes, regulating the complement cascade.³ Complement Factor I gene (CFI, OMIM*217030) codes for a serine protease Factor I (FI) with an important role in CAP regulation. CFI inactivates C3b by cleaving it into iC3b, C3d, and C3dg in the presence of several cofactor proteins.^{S4,S5}

Deficiency of FI is a very rare primary immunodeficiency, inherited as an autosomal recessive trait. It leads to an uncontrolled amplification of C3 cleavage, resulting in a severe secondary C3 deficiency. Complete FI deficiency is strongly associated with severe and recurrent pyogenic infections (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*).^{4,S5}

Here we report, to our knowledge, the first case of a patient with subtotal FI deficiency with homozygous CFI pathogenic variant, which resulted in end-stage renal disease requiring kidney transplantation. This patient exhibited typical pathological findings for C3GN on renal allograft 2 years after transplantation. Strikingly, this untreated recurrent glomerular disease was not associated with infectious episodes and the patient did not develop significant renal impairment after 14 years of follow-up.

CASE PRESENTATION

A 42-year-old white woman with neither family history of renal disease nor consanguinity was referred to our department for a first renal transplantation.

Renal disease manifestations started 6 years earlier with an episode of acute kidney injury and mechanical hemolytic anemia in a context of hypertensive emergency. No kidney biopsy was performed because renal function and proteinuria significantly improved (serum creatinine 1 mg/dl and proteinuria 0.5 g/d) after blood pressure control and administration of renin-angiotensin system blockers. The patient was lost to follow-up. Three years later, she was admitted for end-stage renal disease requiring immediate onset of chronic intermittent hemodialysis. At this time, low C3 and FI levels were found (Table 1). Genetic analysis revealed a homozygous variant located in exon 10 of

Table 1. Complement component assessments and biological parameters before and after renal transplantation

	1999: AKI and HUS	2002: ESRD	2005:	2007: First graft biopsy	2009:	2011:	2019: Last follow-up	
C3 (660–1250 mg/l)	N/A	447	KIDNEY TRANSPLANTATION	574	663	631	731	
C4 (93–380 mg/l)	N/A	281		306	286	281	406	
CH50 (70%–130%)	N/A	80		95	91	106	120	
AP50 (70%–130%)							<10	
FB (90–320 mg/l)	N/A	37		57	84	N/A	N/A	
FH (65%–140%)	N/A	108		111	124	N/A	130	
FI ^a (70%–130%)	N/A	20		19	21	20	24	
sC5b9 <440 ng/ml								1205
CD46 expression (13–19 MFI)	N/A	17		N/A	N/A	N/A	17	
CR1 expression (4–11 MFI)	N/A	N/A		N/A	N/A	N/A	10.3	
FH antibodies	N/A	Negative	Negative	Negative	Negative	Negative		
C3 nephritic factor	N/A	Negative	Negative	Negative	Negative	Negative		
Serum creatinine (mg/dl)	2.05	6.69	0.96	0.92	0.94	0.90		
eGFR (ml/min per 1.73 m ²)	30	7	72	75	72	71		
Proteinuria (g/d)	1.5	5	1.2	1.1	0.51	0.75		
Hemoglobin level (g/dl)	9.8	9	11.6	11.4	12	12.9		
Platelet count (Giga/l)	145	184	154	165	170	183		
LDH (U/l)	400	169	259	245	236	N/A		
Haptoglobin (g/l)	<0.1	1.41	1.25	1.42	1.35	N/A		

AKI, acute kidney injury; AP50, alternative pathway hemolytic assay; CR1, Complement Receptor 1; eGFR, estimated glomerular filtration rate from creatinine by Chronic Kidney Disease–Epidemiology Collaboration formula; ESRD, end-stage renal disease; FB, Factor B; FH, Factor H; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; MFI, mean fluorescence intensity; N/A, data not available; sC5b9, soluble C5b9 plasmatic level.

^aFI antigen level was measured by enzyme-linked immunosorbent assay using polyclonal IgG anti-human Factor I (Calbiochem, Meudon, France). Results are expressed as the percentage of mean values obtained with the reference plasma prepared from 100 healthy blood donors (normal range 100% ± 30%).

CFI gene (c.1071 T>G), resulting in a replacement of an isoleucine (Ile) with a methionine (Met) at position 357 (p.Ile357Met) (Figure 1). This rare variant (variant allele frequency below 0.0001%) is located in the serine protease domain of the light chain of FI (Figure 1). No mutations were found in Factor H, Membrane Cofactor Protein, Factor B, and C3 genes. Complement Receptor 1 (CD35) expression on granulocytes studied by flow cytometry was normal (Table 1).

After 3 years of hemodialysis, the patient underwent kidney transplantation from a deceased donor. Her pretransplantation panel reactive antibody level was 0%. Immunosuppressive regimen included prednisolone, tacrolimus, and mycophenolate mofetil without induction treatment. Posttransplant course was uneventful without infectious episodes or immunological events. Two years after transplantation, proteinuria (1.2 g/d) occurred without impairment of renal function (Table 1). At this time, no donor-specific antibodies were detected. A renal biopsy was performed, and consisted of renal cortex with 17 glomeruli including 2 obsolescent ones. On light microscopy, glomeruli exhibited moderate mesangial expansion and hypercellularity, with glomerular capillary wall remodeling and double contour formation (Figure 2a). Immunofluorescence study showed predominant mesangial and subendothelial C3 deposits (Figure 2b) without evidence for IgG, IgA, or IgM deposits. C4d staining was negative on glomeruli and peritubular capillaries. Persistent proteinuria led us to perform,

2 years later, a second renal biopsy disclosing similar pathological and immunofluorescence results. Electron microscopy (Figure 3) showed subendothelial and paramesangial deposits, without deposits within the glomerular basement membrane. Thrombotic microangiopathy lesions with subendothelial edema in glomerular capillaries were also present. These findings were consistent with C3GN diagnosis on renal graft without arguments for dense deposits disease. Alternative pathway hemolytic assay (AP50) and soluble terminal complement complex (sC5b-9) were repeatedly measured during follow-up. We found that AP50 was low (<10%) and sC5b-9 elevated (649, 1104, and 1205 ng/ml, normal <440) in 2016, 2017, and 2019, respectively. After 14 years of follow-up with renin-angiotensin system blocker treatment, renal function remains unmodified without other specific therapeutic intervention (Table 1). This case description has been approved by our local institutional review board: IRB 412 Mondor no. 00003835 and by the Comité de Protection des Personnes d'Ile de France IV (no. 2016/25NICB).

DISCUSSION

We describe here a very rare case of C3GN occurrence in a kidney transplant recipient with homozygous pathogenic variant in *CFI* gene, potentially implicated in this disease. This case was characterized by a severe phenotype in native kidneys leading to end-stage renal

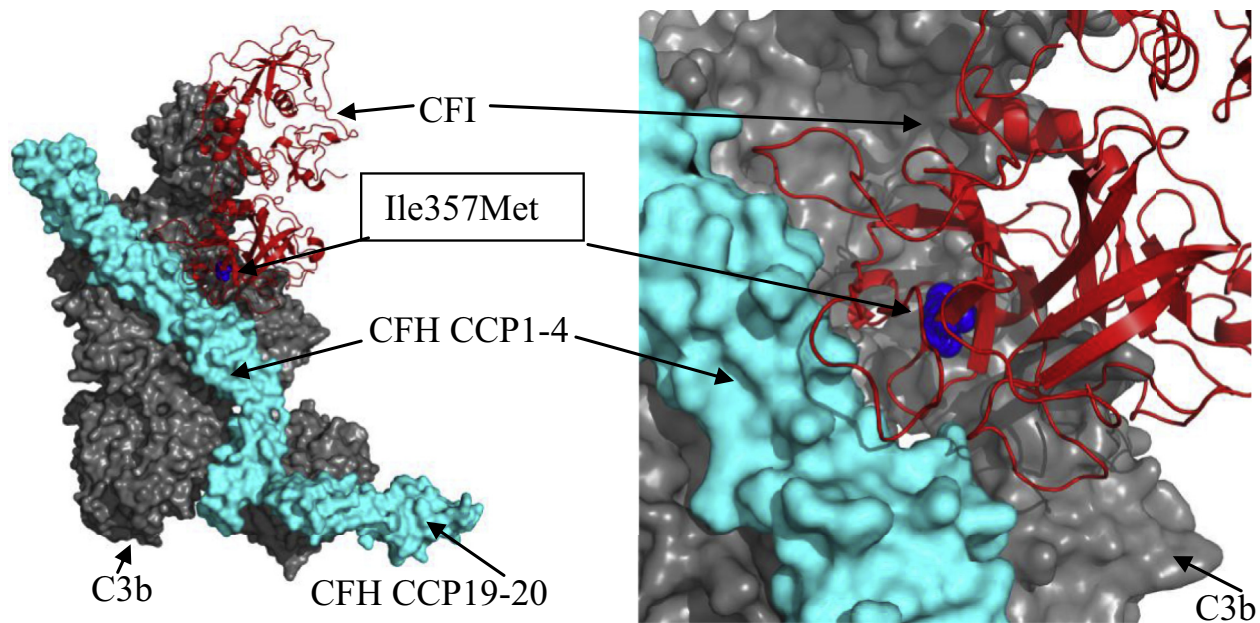


Figure 1. Localization of the mutation p.Ile357Met of Complement Factor I (CFI) on the structure of the triple complex C3b-CFH-CFI. The affected Ile357 is shown in blue spheres. C3b is shown in the gray surface. The regulatory domains of Factor H complement control protein (CCP) 1–4 and CCP 19–20 are depicted in the cyan surface. CFI is represented as a red cartoon. The left panel represents the triple complex; the right panel is a zoom on the region of the mutation. The structure of the triple complex with PDB ID 5032 was used as an input, and the visualization was done by PyMol software.

disease, contrasting with a C3GN with only moderate proteinuria on the renal allograft. To our knowledge, only one observation of total FI deficiency associated with adult-onset immune complex glomerulonephritis (focal and segmental glomerulosclerosis with IgM and IgA focal granular deposits) has been reported.⁵ This

patient had a concomitant CR1 deficiency, whereas CR1 levels in our case were normal.

FI is a key regulator of the complement system that acts by cleaving its substrates C3b and C4b to fragments, unable to sustain complement activation.⁵³ In our patient, the affected isoleucine residue, which is

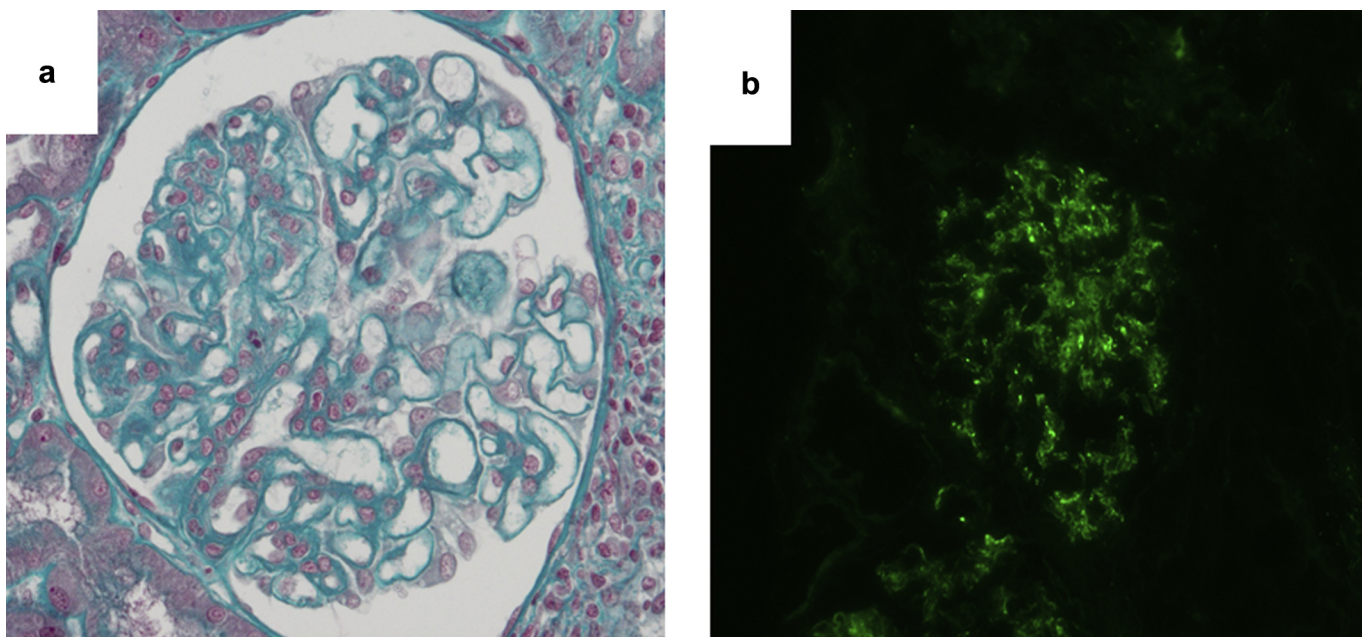


Figure 2. Kidney biopsy findings. (a) Light microscopy analysis: Glomerular lesions consisted in moderate mesangial expansion and hypercellularity, with glomerular capillary wall remodeling and double contour formation (Masson trichrome, original magnification $\times 40$). (b) Immunofluorescence study showing predominant mesangial and subendothelial C3 deposits (anti-C3 fluorescein isothiocyanate-conjugate, original magnification $\times 400$).

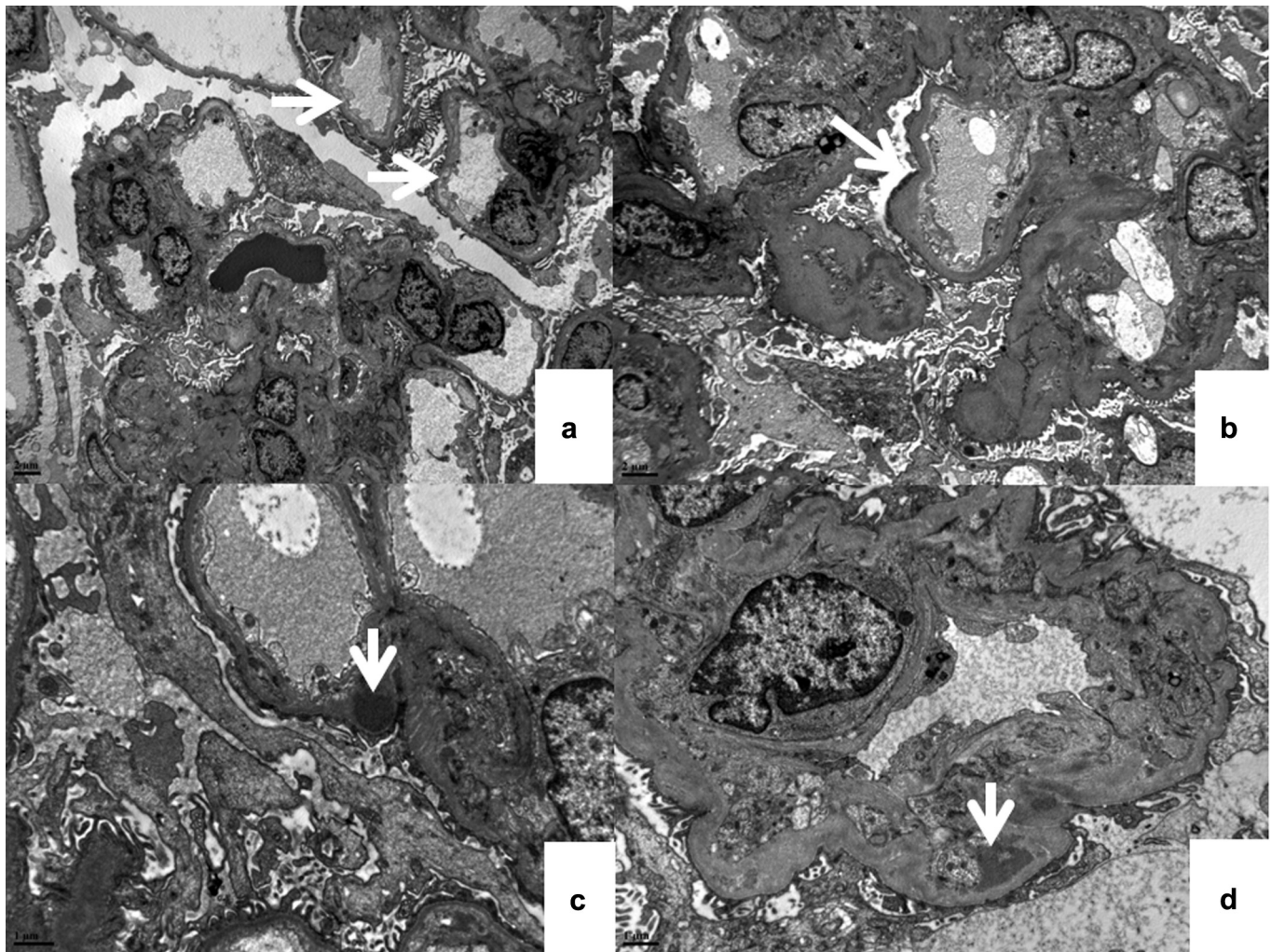


Figure 3. Electronic microscopy examination. (a,b) Thrombotic microangiopathy lesions with subendothelial edema in glomerular capillaries (arrows). (c) Pseudo-hump deposits (arrow). (d) Subendothelial deposits (arrow; original magnification $\times 4000$).

buried in the interior of the serine protease domain, was substituted with a larger, sulfur-containing residue methionine. This substitution is expected to cause alteration of the local protein structure due to clashes of the methionine with the surrounding residues. Although we lack *in vitro* exploration of this *CFI* variant, the molecular modeling suggests that this genetic change can explain the reduced production. The change, though, could still be accommodated by the protein, resulting in a residual secretion and functional activity. Indeed, this genetic change was found in 2 unrelated patients with atypical HUS in a heterozygous state.^{S6,S7} For one of them, the FI levels were reported to be in the normal range, consistent with subtotal deficiency.^{S6} Moreover, the plasmatic C3 levels of our patient were just below the normal range at the time of transplantation and normalized during the follow-up, indicating residual FI activity.

Several cases of near complete FI deficiency have been reported and were found to lead to a systemic consumption of C3, Factor H, and Factor B due to

uninhibited activation of the CAP.⁶ Because of this consumption, opsonization with C3b cannot occur and patients are much more susceptible to recurrent pyogenic infections.^{S8} Strikingly, our patient did not present any severe infectious episode before and after renal transplantation. In the present case, we could hypothesize that remaining activity of the secreted mutant protein was sufficient to prevent complete C3 depletion. CAP overactivation persisted, as evident from the depressed CAP activity (AP50) and the elevated sC5b-9 concentrations in plasma at follow-up, which could contribute to the persistent aggression of the kidney (Table 1).

There have been reports of partial FI deficiency with rare heterozygous variants in patients who suffer from atypical HUS,^{7,S9} C3GN,^{S10} and in age-related macular degeneration.^{S11} More frequently, the variant impairs the synthesis of the protein, explaining the low level of FI in plasma. None of the reported patients with atypical HUS, though, had FI below 30% of the normal range (compared with approximately 20% in this case)

Table 2. Summary of key teaching points regarding GC3 associated with subtotal CFI deficiency

1. Subtotal Complement Factor I deficiency can be revealed by kidney disease even without history of recurrent infections.
2. Posttransplant C3 glomerulonephritis can be associated with good allograft outcome even without specific treatment.
3. Complement assessment and genetic screening are required in cases of severe hypertension associated with hemolytic anemia and acute kidney injury.

despite the frequent association of a consumptive deficiency of C3.^{7,S9}

Unfortunately, no kidney biopsy was performed on native kidneys from our patient but retrospectively the medical history was consistent with end-stage renal disease caused by complement dysregulation. In cases of severe hypertension associated with hemolytic anemia, a pathophysiological interpretation remains complex, because HUS may be a form of complement-mediated disease complicated by hypertensive crisis, or a direct result of hypertension-related mechanical stress on endothelium.^{8,S12} In our patient, the first episode of severe hypertensive flare with mechanical hemolytic anemia in native kidneys suggesting HUS could be retrospectively associated with the subtotal FI deficiency. Moreover, ultrastructural analysis of graft biopsy specimen revealed patterns of thrombotic microangiopathy associated with C3GN. These findings suggest a transition and a close relationship between both pathological entities, which share common molecular mechanisms consisting in dysregulation of the CAP, as previously reported.^{S13}

Nowadays, the use of eculizumab, an anti-C5 monoclonal antibody, is systematically discussed in cases of C3GN and/or HUS recurrence on renal allograft. However, in our case, after 14 years of follow-up, renal function remained unchanged with the exclusive use of renin-angiotensin system blockers, suggesting that eculizumab was not necessary in this case, despite the elevated sC5b-9 concentration. Consistent with this finding, recent studies have shown that C3GN on renal allografts may have heterogeneous long-term renal outcome.^{S14,S15} Similarly, C3GN seems to have a variable course on native kidneys, and eculizumab is potentially more efficient in cases of crescentic rapidly progressive C3GN, whereas the benefit seems limited in non-rapidly progressive forms.⁹ Complement gene variants strongly predict recurrence and graft outcome in adult renal transplant recipients with

atypical HUS, with a higher risk in cases of Complement Factor H mutations than CFI mutations.^{S16} To our knowledge, until now, no CFI homozygous mutations have been described in posttransplantation recurrence of C3GN and HUS. Further studies with large cohorts using the new C3GN classification are needed to more accurately describe the impact of complement genetics and treatment of C3GN posttransplant recurrence.

This case emphasizes the complexity of genotype/phenotype correlation of complement-mediated renal diseases (Table 2). Understanding the mediators of renal disease progression should be the first step to define future optimal therapy.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary References.

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