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A new complement factor B mutation associated with crescentic C3 glomerulopathy; a case report

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ABSTRACT

Background: C3 glomerulopathy is a recently described entity classified as complement-associated glomerular disease.

Case Presentation: We report a case of a 48-year-old man referred to the nephrology department for nephrotic syndrome with rapidly progressive kidney failure, acquired partial lipodystrophy and drusen in Bruch's membrane of the retina. Blood tests showed low C3 and no evidence for autoimmune diseases, monoclonal gammopathy or infection. The renal biopsy revealed a proliferative endocapillary and crescentic glomerulonephritis with glomerular deposits exclusively of C3 and significant interstitial fibrosis. The electronic microscopy was consistent with dense deposit disease. The complement analysis revealed a pathogenic mutation of the complement factor B (CFB) gene not previously described in literature.

Conclusions: The authors report a new mutation of CFB, in a dense deposit disease patient; this finding brings a new insight to the pathogenic pathway of C3 glomerulopathy and possibly to other complement dysregulation associated glomerular diseases. More clinical trials are needed to clarify both the pathogenicity and the optimal treatment for these entities.

Implication for health policy/practice/research/medical education:

The finding of a new mutation of complement factor B together with a haplotype for the complement factor H (CFH) known to confer risk for atypical haemolytic uremic syndrome (AHUS), in a dense deposit disease patient, brings a new insight to the pathogenic pathway of C3 glomerulopathy and possibly to other complement dysregulation associated glomerular diseases. More clinical trials are needed to clarify both the pathogenicity and the optimal treatment for these entities.

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1. Background

C3 glomerulopathy is a recently introduced entity that includes a group of renal diseases characterized by abnormal activation of complement, typically the alternative pathway (1). Pathologically these are characterized by C3 deposition in glomeruli, and absent or scanty immunoglobulin deposition (2), leading to variable glomerular inflammation. C3 glomerulopathy has been further divided into dense deposit disease

(DDD) and C3 glomerulonephritis (C3GN) (3). In light microscopy (LM), mesangial proliferative, membranoproliferative, endocapillary proliferative or crescentic glomerulonephritis may be present. On electronic microscopy (EM), DDD is defined by intramembranous glomerular basement membrane electron-dense deposits, while in C3GN the deposits do not have this dense appearance, but may form ill-defined electron densities in the mesangium or in the

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subendothelial or subepithelial spaces, resembling those seen in immune complex glomerulonephritis (4). The clinical presentation is rather variable and non-specific. It may include hypertension, haematuria, proteinuria (with or without nephrotic syndrome) and often some degree of renal failure. In DDD, acquired partial lipodystrophy (APL), macular drusen and monoclonal gammopathy (MG) may be seen, in addition (3,5). Many patients have evidence of acquired or genetic alternative pathway dysregulation (1). Numerous genetic variants have been described associated to C3 glomerulopathy, namely in the genes coding for complement factor H (CFH), I or B [complement factor B (CFB)], factor H-related proteins (CFHR), C3 or membrane cofactor protein (MCP), in familial or sporadic disease cases (2,4). There are also common variants of complement genes, especially CFH and MCP, which are known to increase the risk of C3 glomerulopathy. It is likely that a multifactorial genetic background contributes to C3 glomerulopathy in individual patients (4).

2. Case Presentation

We report the case of a 48-year-old Caucasian man, having three healthy sons, referred to the nephrology department with a 2 months' evolution rapidly progressive kidney failure. He had smoking habits and a 2 years' history of mild arterial hypertension. No further relevant medical history was known, namely personal or family history of renal disease. At physical examination he presented with lower limb oedema, poorly controlled hypertension, acquired partial lipodystrophy (Figure 1) and the ophthalmologic observation revealed drusen in Bruch's membrane of the retina (Figure 2). The blood tests revealed a normocytic normochromic anaemia (10.9 g/dL), hypoalbuminemia (2.1 g/dL) and hypercholesterolemia (280 mg/dL), a serum creatinine and urea of 5.9 mg/dL and 137 mg/dL respectively, and a quite frankly low C3 (23 mg/dL; range; 90-180)



Figure 1. Acquired partial lipodystrophy.

with normal C4. Urinary dipstick showed protein (+++) and blood (++) and urine microscopy showed red cells. The urinary protein to creatinine ratio was 13 g/g. The remaining tests excluded autoimmune diseases, monoclonal gammopathy and bacterial or viral infections. The factors H, B and I and anti-factor H antibody were determinate and were all quite regular. The renal ultrasound showed normal kidneys' features. Therefore, a renal biopsy was taken. The LM demonstrates complete sclerosis of 7 of the 9 glomeruli and in the two remaining, a proliferative endocapillary glomerulonephritis with cellular crescents (Figure 3). An intense interstitial fibrosis with widespread chronic interstitial infiltrate was diffusely present; a considerable portion of the tubules were atrophy and hyaline thickening of the capillary walls was seen. The immunofluorescence revealed intense capillary wall and mesangial granular deposits exclusively of C3 (Figure 4). EM showed hyperosmophilic, ribbon-like intramembranous deposits, consistent with DDD (Figure 5).

The patient was started on supportive therapy for the nephrotic syndrome, with angiotensin converting enzyme inhibitor, diuretics and statin, but a rapid worsening of renal function requiring haemodialysis, was observed. Given the presence of active lesions in the histology, it was decided to start immunosuppressive therapy with mycophenolate mofetil (500+500 mg, and then 1+1 g) plus intravenous pulses of methylprednisolone (1 g for 3 days) followed by a tapering course of oral

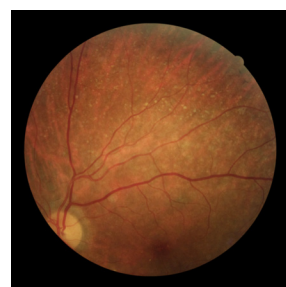


Figure 2. Retinography showing drusen in Bruch's membrane of the retina.

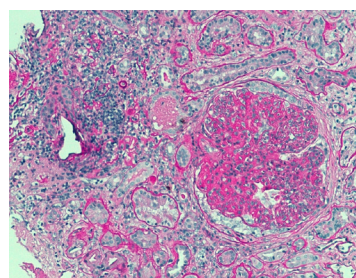


Figure 3. Light microscopy showing proliferative endocapillary glomerulonephritis (Periodic acid-Schiff X200)

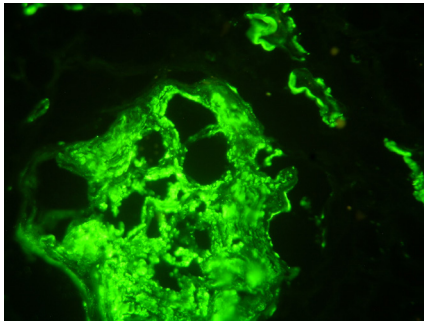


Figure 4. Immunofluorescence showing intense C3 deposits (X400).

prednisone, in an attempt to suppress the acute inflammatory response. Later on, the complement analysis revealed a nonsense pathogenic mutation of the CFB gene - c.1424dupT, p.Ser476Glufs*43, that has never been previously described, in this context, to the best of our knowledge, and a homozygous haplotype for the CFH gene - CFH3-tgtgt - known to confer risk for atypical haemolytic uremic syndrome (AHUS). The patient completed 6 months of therapy without recovering of the renal function, remaining dependent on dialysis. The immunosuppressive drugs were stopped and an arteriovenous fistula constructed after group consultation for dialytic modality decision.

3. Discussion

Dense deposit disease is a rare disease with a poor renal prognosis. Progression to end-stage renal disease, despite treatment, occurs in approximately half of patients with a diagnosis of DDD in 10 years and it is known that renal failure requiring dialysis at the time of presentation is a predictor of progression (3). Dense deposit disease is caused by dysfunction of the complement cascade frequently of genetic origin, more commonly mutations of CFH, CFHR, C3 and MCP, being that mutations of CFB have been rarely described. In this patient a new mutation of CFB, not previously described, was detected, and also a haplotype for the CFH known to confer risk for AHUS. This raises the question whether a common pathologic background is involved in the diseases directed related to impairment of the complement, like thrombotic microangiopathy, as well as a possible role in the pathogenicity of other diseases not directed related to complement dysregulation.

Likewise, the optimal treatment for C3 glomerulopathy remains undefined. Some authors suggest the use of steroids or other immunosuppressants in severe disease with heavy proteinuria, severe disease on biopsy or progressive renal dysfunction (4). We think that in the given patient, the institution of immunosuppressive

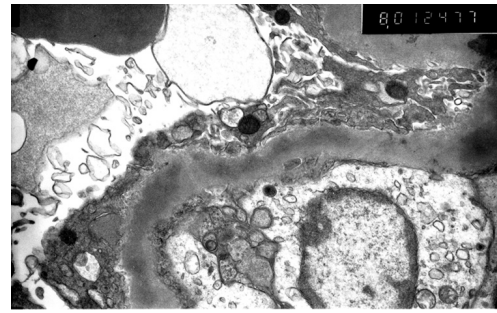


Figure 5. Electron microscopy showing intramembranous electron dense deposits.

therapy is highly debatable, considering the degree of glomerular sclerosis present and the significant interstitial and vascular chronic lesions, which probably contributed to non-response to therapy. There are a number of case reports of the use of eculizumab, however its exact role remains to be defined and, at the time, the data are insufficient to recommend this agent as a first-line agent for the treatment of rapidly progressive disease in C3 glomerulopathy (4). Randomized clinical trials designed to establish the better therapeutic options are undoubtedly needed.

4. Conclusions

Dense deposit disease is a rare disease, related to complement dysregulation, with a poor renal prognosis. We here report a new mutation of CFB together with a haplotype for the CFH, known to confer risk for AHUS, in a DDD patient. This finding brings a new insight to the pathogenic pathway of C3 glomerulopathy and raises the question whether a common pathologic background is involved in all complement dysregulation associated glomerular diseases. More clinical trials are needed to clarify both the pathogenicity and the optimal treatment for these entities.

Authors' contribution

SSC prepared the first draft of the manuscript. ASN reviewed the manuscript. SSC, ARF, ES, PV, ASN and CB; clinical management of the patient. BM, HR, MG and HS; analyzed the pathology data. TF conducted the genetic analysis.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The patient has given his informed consent

regarding this case report.

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