

Case Report

C1q nephropathy: a true immune complex disease or an immunologic epiphenomenon?

Mordi Muorah¹, Manish D. Sinha¹, Catherine Horsfield² and Patrick J. O'Donnell²

¹Department of Paediatric Nephrology, Evelina Children's Hospital and ²Department of Histopathology, St Thomas' Hospital, Guys & St Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, UK

Correspondence and offprint requests to: Patrick J. O'Donnell; E-mail: patrick.odonnell@gstt.nhs.uk

Abstract

We describe a 16-year-old Caucasian boy who presented with steroid-sensitive nephrotic syndrome aged 2 years. His clinical course was one of frequent relapses and severe steroid dependence. To manage this, he was sequentially treated with levamisole, then oral cyclophosphamide before being started on ciclosporin. A renal biopsy performed prior to commencement of ciclosporin confirmed minimal change disease on light microscopy. The immunohistochemistry and electron microscopy findings were in keeping with this. His complement levels were normal and his lupus serology negative. He remained on ciclosporin therapy for 8 years and had two further renal biopsies to detect ciclosporin-induced renal damage. Both biopsies showed evidence of increasing amounts of C1q deposition on immunohistochemistry and the presence of immune deposits on electron microscopy. As he had continued negative lupus serology, this was compatible with a diagnosis of C1q nephropathy. In addition both biopsies had changes compatible with chronic mild ciclosporin nephrotoxicity. This case is the first report describing in detail a paediatric patient with evolving C1q nephropathy who was treated successfully with rituximab. We discuss the role of C1q in this clinicopathological entity and question its significance.

Keywords: C1q nephropathy; nephrotic syndrome; paediatric; rituximab; lupus

Introduction

C1q nephropathy (C1qN) is a renal immunohistopathological disease first described by Jenette and Hipp in 1985 [1]. They described 15 patients with no clinical or serological evidence of systemic lupus erythematosus (SLE) but with extensive glomerular lesions with C1q deposition. They proposed the distinct clinical entity of C1qN with the diagnostic features of (1) lack of clinical and serological evidence of SLE with the (2) presence of dominant or codominant deposition of C1q in mesangium on immunofluores-

cence [1]. On electron microscopy (EM), electron dense deposits were present in the glomerular mesangium in all patients. In addition, all patients in this initial report also had C3, IgG and IgM staining but with reduced intensity.

Since its initial description, numerous case reports and several case series have described patients with C1qN. From the case series alone, we found 241 patients (125 male) with a majority of patients being <18 years of age [1–12]. Over 20 years later, C1qN continues to be a controversial clinical entity with no clear evidence of its pathogenic role and its clinical utility [4]. We describe here a patient with severe steroid-dependent nephrotic syndrome (SDNS) who had three renal biopsies; the first confirming minimal change disease but subsequent biopsies documenting progressive C1qN as suggested by increasing C1q deposition both on immunohistochemistry and EM.

Case report

We describe the case of a 16-year-old Caucasian boy HK, who at age 2 years presented with nephrotic syndrome: generalized oedema, microscopic haematuria, hypoalbuminaemia at 14 g/l and nephrotic range proteinuria of 3.4 g protein in a 24-h urine sample. There was evidence of hypovolaemia with raised blood pressure at 140/90 mmHg and renal dysfunction with elevated urea at 20.9 mmol/l and creatinine 105 µmol/l. His plasma complement levels for C3 and C4 were normal, and antinuclear antibody levels were also normal. His antistreptolysin O titre was not elevated. His hypovolaemia was treated with 1 g/kg of 20% human albumin solution with consequent improvement of his renal dysfunction and hypertension. On commencement of oral prednisolone therapy at 60 mg/m²/day, he achieved remission in 8 days and was weaned off steroids over the following 2 months. His clinical course was, however, one of frequent relapses with subsequent steroid dependence. To manage his SDNS more effectively and to reduce side effects of steroids, steroid-sparing agents were added to his therapy. He was sequentially treated with levamisole, and then with oral cyclophosphamide before being commenced

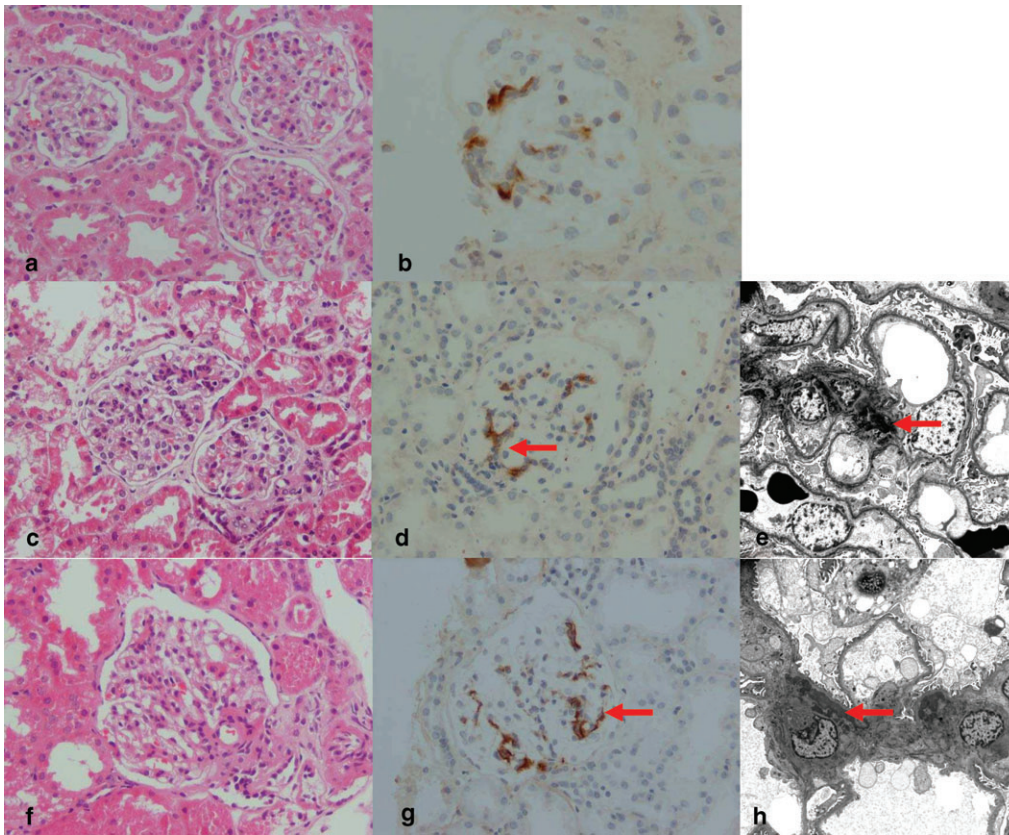


Fig. 1. (a) First biopsy: normocellular glomeruli (haematoxylin and eosin; $\times 200$). (b) First biopsy: weak mesangial staining for C1q (C1q immunohistochemistry; $\times 400$). (c) Second biopsy: mild increase in mesangial cellularity (haematoxylin and eosin; $\times 200$). (d) Second biopsy: dominant mesangial staining of C1q (C1q immunohistochemistry; $\times 200$). (e) Second biopsy: mesangial electron dense deposits (uranyl acetate/lead citrate $\times 5000$). (f) Third biopsy: mesangial proliferation (haematoxylin and eosin; $\times 200$). (g) Strong mesangial staining of C1q (C1q immunohistochemistry; $\times 200$). (h) Large and partly confluent mesangial electron dense deposits (uranyl acetate/lead citrate $\times 5000$). Arrows in the figure indicate areas of C1q deposition.

on ciclosporin three and a half years after initial presentation with nephrotic syndrome.

A percutaneous renal biopsy and measurement of true glomerular filtration rate (GFR) using the plasma clearance of Inutest[®] method were performed just prior to commencement of ciclosporin therapy. Light microscopy findings at this point were consistent with minimal change disease. There were no proliferative or sclerosing lesions. There were some small flecks of C1q involving the glomerular mesangium on immunohistochemistry, but no corresponding electron dense immune deposits were found on EM (Figure 1a and b). His Inutest[®] GFR was normal at 101 ml/min/1.73 m². His complement levels remained normal, and his lupus serology was negative. Following commencement of ciclosporin, he had infrequent relapses and managed to stop prednisolone therapy completely for a period of 18 months. Attempts to stop ciclosporin though were unsuccessful, and he therefore continued with ciclosporin therapy for a total of 8 years and had two further renal biopsies as part of surveillance to detect ciclosporin-induced renal damage.

The second renal biopsy was performed 3 years after commencement of ciclosporin therapy. Light microscopy showed many normal glomeruli but some showed a mild/borderline increase in mesangial cellularity. The immunoperoxidase staining now showed faint staining for IgM

and C1q involving the glomerular mesangium with dominance of the C1q signal over that of the IgM. EM was not performed at the time that this biopsy was submitted but was performed when the third biopsy from this patient was submitted (see below). EM of the second biopsy confirmed corresponding nodular and homogeneous immune electron dense deposits in the mesangium (Figure 1c–e).

It is reasonable to suggest if EM had been performed at the time of receipt of the second biopsy that the diagnosis of C1qN would have been confirmed at that stage.

His complement levels remained normal, and his lupus serology remained negative. Two Inutest[®] GFRs were performed during this period, the first a year prior to and the second at the time of the second renal biopsy. Both were normal with measurements at 87 and 90 ml/min/1.73 m² respectively.

A third percutaneous renal biopsy was performed 7 years after commencement of ciclosporin therapy. Light microscopy findings revealed some evidence of ciclosporin toxicity with some vacuolation and protein resorption droplets of the lining epithelial cells in the proximal tubule as well as a few small foci of mild tubular atrophy.

Light microscopy of this biopsy showed diffuse mesangial proliferation without segmental (endocapillary) proliferation that was more evident and diffuse than the mild mesangial hypercellularity noted in the previous biopsy. In

addition, this biopsy showed easily identifiable and small mesangial fuchsinophilic deposits on trichrome stains. Immunohistochemistry showed very strong dominant staining for C1q but also less dominant staining for C3 and IgM in the glomerular mesangium and of a few extra-mesangial capillary wall deposits. EM confirmed corresponding immune electron dense deposits including a few isolated and peripheral ribbon-like sub-endothelial electron dense deposits (Figure 1f–h). These findings were diagnostic of C1qN.

A repeat Inutest GFR at the time of the third biopsy was measured at 97 ml/min/1.73 m². His serum complement levels continued to remain normal, and his lupus serology remained negative.

Following the findings of the third biopsy, all previous biopsies were reviewed again individually by renal histopathologists CH and PJO'D to look for any previous evidence of C1q staining on immunostaining or deposits on EM. No immune deposits were found on EM of the first biopsy, but they were found when an ultrastructural evaluation of the second biopsy was performed. The dominance of the C1q staining and the presence of definable electron dense immune deposits on the second biopsy confirmed the diagnosis. It is possible that the occasional segmental distribution of immune deposits under this condition was the reason why they were not sampled in the EM evaluation of the first biopsy.

Following detection of mild chronic ciclosporin-induced nephrotoxicity and ongoing SDNS, ciclosporin was stopped and substituted with mycophenolate mofetil (MMF) at age 12 years. He unfortunately went on to have several relapses whilst on MMF therapy and needed increasing doses of prednisolone in addition, to maintain him in remission. Ciclosporin was therefore recommenced at age 15 years. HK remained in remission over the first 12 months after recommencement of ciclosporin, but this was only possible with the additional need for high doses of prednisolone to maintain remission. More recently, he has had clinical relapses despite maintaining therapeutic ciclosporin drug levels and continuing need for high-dose alternate day steroids. An Inutest[®] GFR performed at age 16 years and 8 months was measured at 82 ml/min/1.73 m² now after >9 years of ciclosporin therapy. Of concern, this had reduced from a previous measurement of 99 ml/min/1.73 m² performed 15 months earlier. He remains normotensive on no anti-hypertensive medications. A fourth renal biopsy was attempted but unsuccessful because of technical difficulties. Given the lack of further clinical response to ciclosporin and evidence of its nephrotoxicity, he was given anti-CD20 monoclonal antibody Rituximab (two doses at 750 mg/m² each, given two weeks apart). Ciclosporin was stopped 2 weeks after the second infusion of rituximab. Seven months later, he remains in remission on minimal alternate day steroid therapy alone.

Discussion

We report here the clinical course of a paediatric patient who presented with steroid-sensitive nephrotic syndrome and make the interesting observation of the evolution of

C1qN disease as demonstrated by increasing deposition of C1q on serial renal biopsies despite ongoing immunosuppressive therapy. The patient reported here showed no glomerular changes in the findings on light microscopy of the initial biopsy, but the two subsequent biopsies showed increasing mesangial hypercellularity—mesangial proliferation with serial biopsies showing increasing long-term side effects of ciclosporin therapy. There were no lesions of focal segmental glomerular sclerosis (FSGS), and no endocapillary proliferative lesions were seen in any of the three biopsies. The immunostaining showed an initial absence but subsequent increase and dominant intensity of staining with C1q. EM confirmed this pattern with the identification of immune deposits in the glomerular mesangium. These findings were observed over a 10-year period of severe SDNS, and three renal biopsies were performed 3, 6 and 10 years after initial presentation. This pattern of a gradual increase in deposition from no detectable C1q deposits to large intense and dominant deposits in the glomerular mesangium despite ongoing treatment and marked clinical response has not been described before.

This observation raises an obvious question of the pathophysiological role of C1q immune deposits in propagating C1qN. The exact pathophysiological mechanism by which C1q deposition is likely to cause disease is yet to be completely elucidated, although C1q is known to bind strongly to laminin, a basement membrane protein [13], and C1q receptors play a role in enhancing binding of immune complexes to human mesangial cells [14]. The C1q complement protein itself on binding to immunoglobulin forms the C1 protease in combination with C1r and C1s, and this activates the classical complement cascade culminating in the membrane attack complex, C5b-9 [14].

The histopathological findings described in patients with C1qN have usually varied with minimal change disease and FSGS being reported most commonly [2,4,6–8,10]. In a study by Markowitz *et al.*, as many as 17 out of the 19 patients with C1qN had FSGS on renal histopathology. A recent paper by Roberti *et al.*, however, showed on histopathology a preponderance of children with diffuse mesangial proliferation with or without segmental sclerosis [11]. On immunofluorescence, C1q can often be found in the context of a 'full house' picture whereby other immunoglobulins IgA, IgG, IgM and complement components of the alternative pathway C3 are also seen although these are not the dominant stain [7].

This case also raises questions regarding the clinical significance of C1q immune deposits. Since its initial description there have been numerous published case series and several case reports of patients with this condition [2–12]. We have summarized the findings of the case series in Table 1. It is interesting to note that dominant C1q immune deposits and therefore C1qN have been observed with almost any clinical presentation. Although the initial reports were of patients with severe proteinuria, subsequent reports have highlighted the variable presentation in patients with C1qN [2–12]. Patients with C1qN have usually been observed to present with a variable degree of proteinuria but a recent paediatric series reporting from Japan observed school children with asymptomatic microscopic haematuria [8,10]. This was picked up on routine

Table 1. Summary of published series of C1q nephropathy

Ref, author (year)	n (M)	Age (range in years)	Presenting features (numbers presenting)	Histological findings	Management	Follow-up (range)
[1], Jeanette (1985)	15 (8)	17.8 (14–27)	Proteinuria (9) and proteinuria with haematuria (6)	MCD (2), mesangial hypercellularity (3), FPGN (5), DPGN (3) and inadequate specimens for full light microscopic diagnosis (2)	No treatment (6) and steroids (9)	No definite resolution in proteinuria in all patients (1–19 months of follow-up)
[2], Iskandar (1991)	15 (5)	9.1 (2–16)	NS (9), glomerulonephritis (3) and nephritic/NS (3)	No histological glomerular alterations (8) and FSGS ± mesangial proliferation (7)	No treatment (6) and steroids (9)	Remission (3), SDNS (2), FRNS (2) and ESRD (2) (4 months–5 years of follow-up in 13/15 patients)
[3], Davenport (1992)	4 (1)	47.8 (23–72)	NS (4)	MCGN (1), membranous nephropathy (1), FSGS and FPGN (1) and DPGN (1)	No treatment (3) and steroids and ciclosporin (1)	Resolution in all 4 patients (1.7–19 years of follow-up)
[4], Markowitz (2003)	19 (5)	24.2 (3–42)	NP (15) and haematuria (3)	FSGS (17) and MCD (2)	Steroids (7), steroids and ciclosporin (4), steroids, ciclosporin and cyclophosphamide (1). Several patients also received ACEi or ARB	Complete resolution (1), partial resolution (6), no resolution (4), CKD (4 of whom 2 reached ESRD) (3–81 months of follow-up in 16/19 patients)
[5], Sharman (2004)	9 (2)	26 (19–63)	Haematuria (1), proteinuria and haematuria (5), NS (1) and CKD (2)	Crescentic glomerulonephritis (1), DMP (3), FPGN (2) and membranous and mesangial proliferation (3)	No treatment (5), steroids (1), steroids and azathioprine (1), steroids, cyclophosphamide and azathioprine (2)	Persistent proteinuria (7 of which 2 had CKD), ESRD (1) and death of cardiovascular cause (1) (0.1–9 years of follow-up)
[6], Kersnik (2005)	12 (4)	10.2 (4–16)	Proteinuria and haematuria (3), NS (8), CKD (1)	MCD (4), FSGS (6 of which 4 also had DMP) and focal glomerulonephritis (2)	No treatment (1), steroids and cyclophosphamide (6), steroids, cyclophosphamide and other immunosuppressive agents with or without ACEi (2) and ACEi alone (3)	Complete resolution of NS (4), partial remission (1), no change (5), ESRD (2) (0.5–17 years)
[7], Lau (2005)	20 (11)	10.9 (0.9–15.6)	Proteinuria (12) and NS (8 of which 3 also had chronic kidney disease)	FSGS (8), MCD (6), global sclerosis (3) and mesangial proliferation (3)	No treatment (8), ARB and/or ACEi (5); ACEi and ciclosporin (2), steroids and ACEi (4), steroids and ciclosporine (1)	Kidney survival at 95% and 78% at 1 and 5 years respectively, ESRD (4)
[8], Fukuma (2006)	30 (18)	10.5 (3–15)	Haematuria (18) and NS (12)	MCD (22), FSGS (2) and FPGN or DPGN (6)	No treatment (14), steroids (13) and steroids and ciclosporin (3)	Complete resolution (11), persistent abnormal urinary sediment (9), FRNS (8), ESRD (2), disappearance of C1q deposits on subsequent biopsy (2) (3–15 years of follow-up)

[9], Vizjak (2008)	72 (49)	(2–66)	NS or nephrotic range proteinuria (34), non-nephrotic range proteinuria (27), hypertension (35), haematuria (50), CKD (33) and (some of the patients had more than one presenting symptom)	No lesions (27), FSGS (11), proliferative glomerulonephritis (20), TIN (6), TBMD (3), ARPKD (1), medullary cystic disease (1), benign hypertensive nephrosclerosis (1), hantavirus nephropathy (1)	Steroids (21 of which 10 also received cyclophosphamide). Also in this group of 21 patients, some patients also received one or more of cyclosporine, azathioprine, MMF and tacrolimus	Complete resolution (17), partial remission of NS (8), stable renal disease (11), CKD (4) and ESRD (8) (0.3–21 years of follow-up)
[10], Hisano (2008)	61 (33)	19.6 (1–67)	Asymptomatic urinary abnormalities (36) and NS (25)	MCD (46), MCGN (7) and FSGS (8)	Steroid and or cyclosporine (all patients with nephrotic syndrome and 9 patients in the asymptomatic group)	Complete resolution (18; 10 in the asymptomatic group and 8 with NS), FRNS (13) and CKD in 3 patients with FSGS (3.0–18.0 years of follow-up)
[11], Roberti (2009)	14 (7)	10.7 (1–18)	NS (10 in total of which 2 also had haematuria and 2 had hypertension), gross haematuria (2), asymptomatic proteinuria and hypertension (2), one with NS subsequently had a renal transplant	DMP (12) of which 3 also had SS and membranous nephropathy (2)	No treatment (1), steroids (1), ACEi (2), ACEi and steroids (7 of which 4 had tacrolimus and/or MMF)	Complete resolution (8), partial remission (4) and FRNS (4) (0.25–5.5 years of follow-up)
[12], Wong (2009)	9 (5)	2.7 (1.3–15)	NS (9), hypertension (1)	Not given	Steroids and calcineurin inhibitors (9 of which 4 also received cyclophosphamide and 3 MMF) and ACEi (2)	Complete resolution (9) (18–113 months)

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockade; ARPKD: autosomal recessive polycystic kidney disease; CKD: chronic kidney disease; DMP: diffuse mesangial proliferation; DPGN: diffuse proliferative glomerulonephritis; ESRD: end-stage renal disease; FPGN: focal proliferative glomerulonephritis; FRNS: frequently relapsing nephrotic syndrome; FSGS: focal and segmental glomerulonephritis; MCD: minimal change disease; MCGN: mesangiocapillary glomerulonephritis; MMF: mycophenolate mofetil; NP: nephrotic range proteinuria; NS: nephrotic syndrome; SDNS: steroid-dependant nephrotic syndrome; SS: segmental sclerosis; TBMD: thin basement membrane disease; TIN: tubulointerstitial nephritis.

screening and was a presenting sign in the majority of cases [8,10].

A recent large series by Vizjak *et al.* reported 72 patients over a 20-year period (1985–2005) from Slovenia [9]. In this report, there were eight patients with a clinical presentation of nephrotic syndrome (seven with MCD and one with FSGS) who underwent repeat renal biopsies. Four of these seven patients with initial minimal change disease showed ongoing MCD, two developed mild mesangial proliferation and one developed FSGS. The patient with initial FSGS had no change on repeat biopsy. One of the patients with initial MCD showed continuing MCD on repeat biopsy but with negative C1q staining 1 year following the first biopsy. Most repeat biopsies in this series were performed 0.5–2 years after the initial biopsy but in two patients 13 and 16 years following the first biopsy. The authors concluded that immune complex deposition probably influences the course of the disease although details of the clinical course of the nine patients described above are not given. It is interesting to note that our patient showed no primary histopathological findings on light microscopy on the initial biopsy but showed increasing mesangial hypercellularity on two subsequent biopsies together with the detection of increasing intensity of C1q immune deposit on immunohistochemistry and the appearance of immune electron dense deposits on EM in the two later biopsies. The histological findings in themselves were non-diagnostic, but the immunohistochemistry and EM were crucial in confirming the diagnosis in this patient. As described in the case history in our patient, the appearance of C1q complexes did not seem to have any obvious bearing with the clinical course of the nephrotic syndrome.

To our knowledge, this is the first patient with C1qN to be treated successfully with rituximab, a chimeric anti-human CD20 antibody [15]. Rituximab is being increasingly reported to induce remission in patients with both steroid-sensitive and steroid-resistant nephrotic syndrome [16–18]. The pathogenesis of childhood idiopathic nephrotic syndrome remains poorly understood. T-lymphocytes have been implicated in its pathogenesis for years, but recent reports of the efficacy of rituximab in idiopathic nephrotic syndrome suggest a probable role for B-lymphocytes as well. The favourable response of our patient to rituximab offers clinicians a useful therapeutic agent in the management of patients with C1qN who present with severe SDNS.

Did our patient have C1qN at the time of initial presentation despite the absence of any definable C1q immune deposits? This is unlikely given the essential diagnostic criteria for C1qN described earlier. In addition to our patient, the recent report by Vizjak *et al.* described three patients with the initial diagnosis of nephrotic syndrome with minimal change nephropathy but absent C1q nephropathy who subsequently developed C1q deposition on immunofluorescence [9]. This observation has also been made by Hisano *et al.* in four patients (two with nephrotic syndrome and two with haematuria and proteinuria) [8,10]. An analogy can be drawn here with cases of evolution of IgA nephropathy reported in a paper by Julian *et al.* in 1991 [19]. The authors describe four adults presenting with macroscopic haematuria with a diagnosis of IgA nephropathy made on a subsequent biopsy performed 9 months to 4 years from

presentation. Previous renal biopsies had not shown any evidence of IgA deposits on immunofluorescence. Interestingly, in these second biopsies, there was also evidence of progression of the pathological process on light microscopy suggesting a pathophysiological role of the IgA deposition in these cases.

Finally, the disappearance of C1q lesions on a long-term follow-up has also been described in the literature [8–10]. This coupled with the appearance of C1q deposits some time after initial presentation as in our case further questions the role of C1q deposits in this clinical entity. Certainly the emergence of C1q deposits after a number of years in a patient presenting with nephrotic syndrome with mild changes of microscopic pathological progression in histology makes the theory of it being an immune complex-mediated glomerulopathy less likely [2]. The other possible explanation could be that the disease we describe here and the many others described in the literature previously, histologically and immunohistochemically are in keeping with C1qN, but really are different diseases with different pathological processes, and C1q immune deposits are merely observed on immunofluorescence.

The myriad clinical presentations, histological findings and outcomes of these patients raise the question whether C1qN constitutes one disease or whether the observation of C1q antibody in disease is merely an epiphenomenon.

Conflict of interest statement. None declared.

References

- Jennette JC, Hippi CG. C1q nephropathy: a distinct pathologic entity usually causing nephrotic syndrome. *Am J Kidney Dis* 1985; 6: 103–110
- Iskandar SS, Browning MC, Lorentz WB. C1q nephropathy: a pediatric clinicopathologic study. *Am J Kidney Dis* 1991; 18: 459–465
- Davenport A, Maciver AG, Mackenzie JC. C1q nephropathy: do C1q deposits have any prognostic significance in the nephrotic syndrome? *Nephrol Dial Transplant* 1992; 7: 391–396
- Markowitz GS, Schwimmer JA, Stokes MB *et al.* C1q nephropathy: a variant of focal segmental glomerulosclerosis. *Kidney Int* 2003; 64: 1232–1240
- Sharman A, Furness P, Feehally J. Distinguishing C1q nephropathy from lupus nephritis. *Nephrol Dial Transplant* 2004; 19: 1420–1426
- Kersnik LT, Kenda RB, Avgustin CM *et al.* C1Q nephropathy in children. *Pediatr Nephrol* 2005; 20: 1756–1761
- Lau KK, Gaber LW, Delos Santos NM *et al.* C1q nephropathy: features at presentation and outcome. *Pediatr Nephrol* 2005; 20: 744–749
- Fukuma Y, Hisano S, Segawa Y *et al.* Clinicopathologic correlation of C1q nephropathy in children. *Am J Kidney Dis* 2006; 47: 412–418
- Vizjak A, Ferluga D, Rozic M *et al.* Pathology, clinical presentations, and outcomes of C1q nephropathy. *J Am Soc Nephrol* 2008; 19: 2237–2244
- Hisano S, Fukuma Y, Segawa Y *et al.* Clinicopathologic correlation and outcome of C1q nephropathy. *Clin J Am Soc Nephrol* 2008; 3: 1637–1643
- Roberti I, Baqi N, Vyas S *et al.* A single-center study of C1q nephropathy in children. *Pediatr Nephrol* 2009; 24: 77–82
- Wong CS, Fink CA, Baechle J *et al.* C1q nephropathy and minimal change nephrotic syndrome. *Pediatr Nephrol* 2009; 24: 761–767
- Bohnsack JF, Tenner AJ, Laurie GW *et al.* The C1q subunit of the first component of complement binds to laminin: a mechanism for the deposition and retention of immune complexes in basement membrane. *Proc Natl Acad Sci* 1985; 82: 3824–3828

14. van den Dobbelaen ME, van der Woude FJ, Schroeijers WE *et al.* Both IgG- and C1q-receptors play a role in the enhanced binding of IgG complexes to human mesangial cells. *J Am Soc Nephrol* 1996; 7: 573–581
15. Pescovitz MD Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. *Am J Transplant* 2006; 6: 859–866
16. Gilbert RD, Hulse E, Rigden S. Rituximab therapy for steroid-dependent minimal change nephrotic syndrome. *Pediatr Nephrol* 2006; 21: 1698–1700
17. Bagga A, Sinha A, Moudgil A Rituximab in patients with the steroid-resistant nephrotic syndrome. *N Engl J Med* 2007; 356: 2751–2752
18. Guignon V, Dallochio A, Baudouin V *et al.* Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. *Pediatr Nephrol* 2008; 23: 1269–1279
19. Julian BA, Cannon VR, Waldo FB *et al.* Macroscopic hematuria and proteinuria preceding renal IgA deposition in patients with IgA nephropathy. *Am J Kidney Dis* 1991; 17: 472–479

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