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C3 glomerulonephritis: two pediatric cases

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C3 glomerulopathy defines a group of diseases characterized with deposition of C3 alone in the glomeruli in the absence of deposition of immunoglobulin or other complement products. These diseases include dense deposit disease, type 1 membranoproliferative glomerulonephritis (MPGN), familial type 3 MPGN, familial C3 glomerulonephritis associated with mutation in complement factor H related protein 5 and idiopathic C3 glomerulonephritis. Recently, dysregulation of the complement system has been accused in the disease pathogenesis. In this manuscript, two pediatric cases of probable C3 glomerulonephritis according to clinical and renal biopsy findings are presented. One of the cases had presented with the nephrotic-nephritic syndrome and the other with macroscopic hematuria, and both had good prognosis.

Keywords: glomerulonephritis, membranous; immunoglobulins; infant; child

INTRODUCTION

Idiopathic C3 glomerulonephritis (i-C3-GN) has quite a low prevalence in children (1,2). Clinical picture may vary from isolated hematuria to terminal renal failure (2). The exact pathogenesis is unknown. However, recently it has been reported that i-C3-GN is associated with dysregulation of the complement system (3). The diagnosis is established with the demonstration of mesangial and/or subendothelial isolated C3, in the absence of signs of membranoproliferative glomerulonephritis in kidney biopsy or any underlying disease (3-5).

The clinical course and treatment of i-C3-GN is not known exactly; however, factors associated with poor prognosis include severe proteinuria, hypertension, resistance to steroid therapy in terms of clinical findings, severe mesangial proliferation, glomerular sclerosis, and tubulointerstitial injury in terms of biopsy findings (2,6-8).

In recent years, CFHR5 (complement factor H related protein 5) mutations were identified in families of Cypriot origin with cases of mesangial C3 glomerulopathy. Although the clinical entity, familial nature, and prognostic significance of i-C3-GN are not known exactly, the same entities of familial C3-GN with CFHR5 mutations were clearly defined (9,10).

Two pediatric cases of probable i-C3-GN presenting with different symptoms are described as a rare disease in the pediatric age group.

CASE 1

A 20-month-old male patient presented with complaint of blood in urine. His past medical history was characterized by nephrotic syndrome due to proteinuria, hypoalbuminemia, hyperlipidemia determined 40 days before upon evaluation of swelling in the legs, without macroscopic hematuria, azotemia, and hypertension. Prednisolone therapy had been initiated; however, kidney biopsy was performed due to the emergence of macroscopic hematuria, azotemia, hypertension, and demonstration of normal complement (C3, C4) levels. Nothing significant was noted in his medical history. Family history revealed consanguinity between the parents; physical examination revealed hypertension and extensive edema. Laboratory testing showed urine density of 1005, pH 5.5, protein (4+), blood (4+) with several dysmorphic erythrocytes on urine analysis. The rate of urine protein/creatinine was 26.2 mg/mg. Blood biochemistry showed blood urea nitrogen (BUN) of 7.7 mmol/L, creatinine 53.9 µmol/L, albumin 29 g/L, triglycerides 4.8 mmol/L,

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total cholesterol 6.7 mmol/L, high density lipoprotein 1.0 mmol/L, and low density lipoprotein 12.2 mmol/L. Anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), and viral serology were negative, and the levels of anti-streptolysine O (ASO), IgA, and C3-C4 were normal. Renal echogenicity was enhanced bilaterally on renal ultrasonography (US). Additionally, light microscopy of the kidney biopsy specimen demonstrated a mild degree of mesangial cell proliferation and focal tubulointerstitial changes, while immunofluorescent microscopy (IFM) revealed mesangial C3 (3+) deposition. The patient was diagnosed with C3-GN according to these findings. Cyclophosphamide, dipyridamole and angiotensin converting enzyme (ACE) inhibitor were added to treatment, since no response had been obtained with prednisolone (2 mg/kg/day). Rapid improvement was observed in clinical and laboratory findings. Cyclophosphamide was stopped in third month due to the risk of toxicity, while dipyridamole and ACE inhibitor therapies were discontinued in sixth month since proteinuria and hematuria were improved completely. Remission persisted at the last 24-month follow up visit.

CASE 2

A five-year-old girl presented with complaint of bloody urination that had first occurred two years before and repeated on several occasions. Medical history and family history were unremarkable. Physical examination proved normal. Complete urine examination demonstrated protein (1+), blood (4+), abundant dysmorphic erythrocytes and urinary protein excretion of 10.2 mg/m^2/hour. Additionally, the levels of BUN, creatinine, electrolytes, C3-C4, ASO and IgA were normal, and the patient was negative for ANA and ANCA. Renal and renovascular Doppler US imaging were also normal and kidney biopsy was performed to assess macroscopic hematuria and proteinuria of non-nephrotic level. In kidney biopsy there were 63 glomeruli, 18 of which had immature appearance and 5 showed global sclerosis. The other glomeruli showed moderate mesangial proliferation; there was no glomerular inflammation and extracapillary proliferation (Figure 1). There was mild tubular atrophy and interstitial fibrosis. IgG, IgA, IgM and C1q were negative but there was mesangial ++C3 staining on direct immunofluorescence microscopy (Figure 2) and only mesangial electron dense deposits were observed on electron microscopy (Figures 3 and 4). In the light of these findings, treatment with ACE inhibitor was initiated with a pre-diagnosis of C3-GN to treat the proteinuria of non-nephrotic level. Proteinuria was observed to regress with treatment. One episode of recurrent macroscopic hematuria was observed during a 21-month period of follow-up; however, no increase was observed in the level of proteinuria.

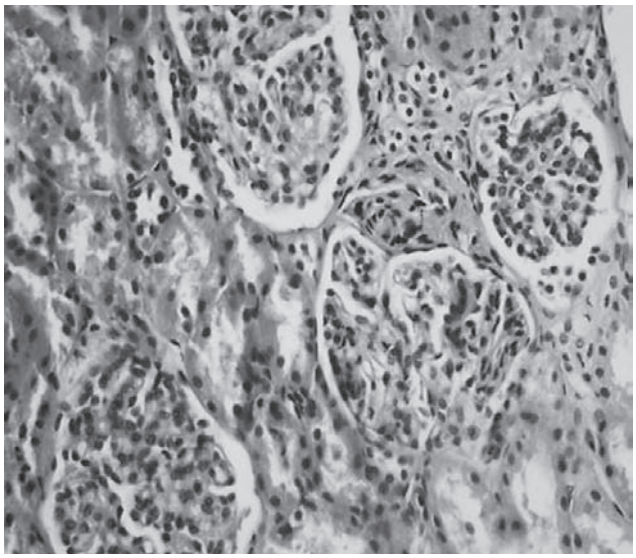

FIGURE 1. Case 2: 1- mesangial proliferation in three glomeruli; note the immature glomeruli on the left side (periodic acid-Schiff staining, X200).

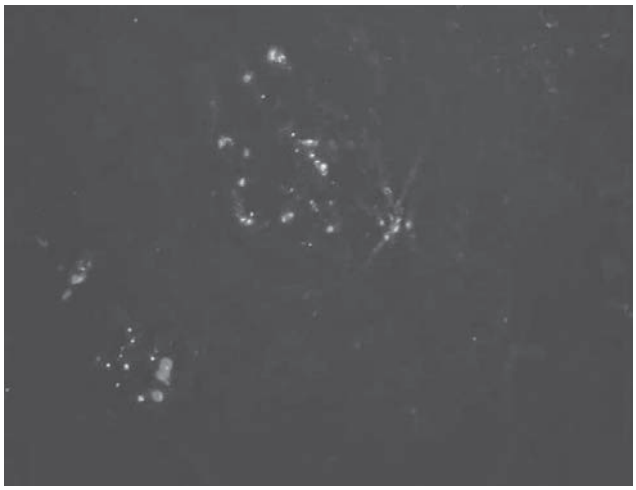

FIGURE 2. Case 2: ++ of mesangial C3 deposition (DIF original magnification X400).

DISCUSSION

C3 glomerulopathy is a common term for a group of diseases characterized by isolated C3 deposition in renal tissue. These diseases include dense deposit disease (DDD), MPGN type 1, familial MPGN type 3, CFHR5 nephropathy and i-C3-GN (3). Additionally, isolated C3 deposition may also occur secondary to several diseases including autoimmune, neoplastic and inflammatory diseases.

I-C3-GN is a rare form of C3 glomerulopathies; its exact pathogenesis is not known and it is quite difficult to explain the isolated C3 deposition in the absence of immunoglobulins (Ig). The following potential mechanisms have been reported: local C3 synthesis by mesangial cells, excessive C3

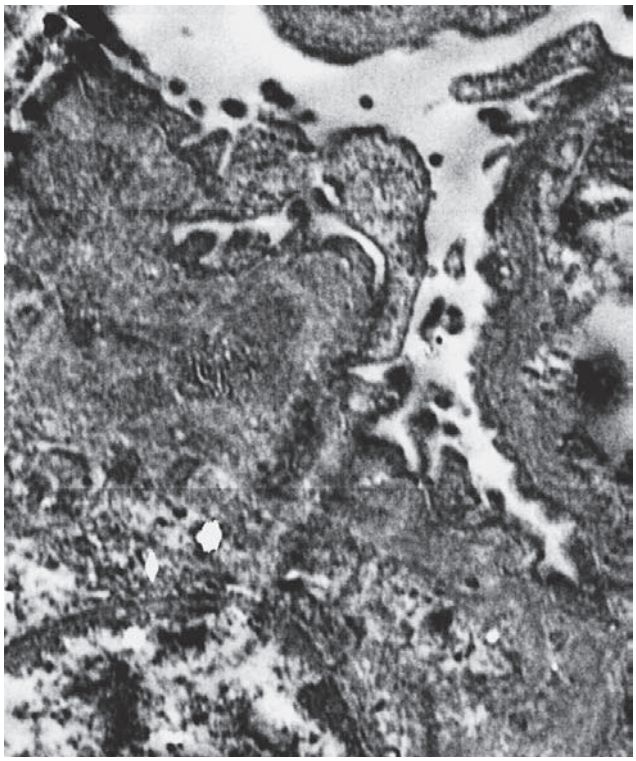

FIGURE 3. Case 2: Mesangial electron dense deposits (EM, X6000).

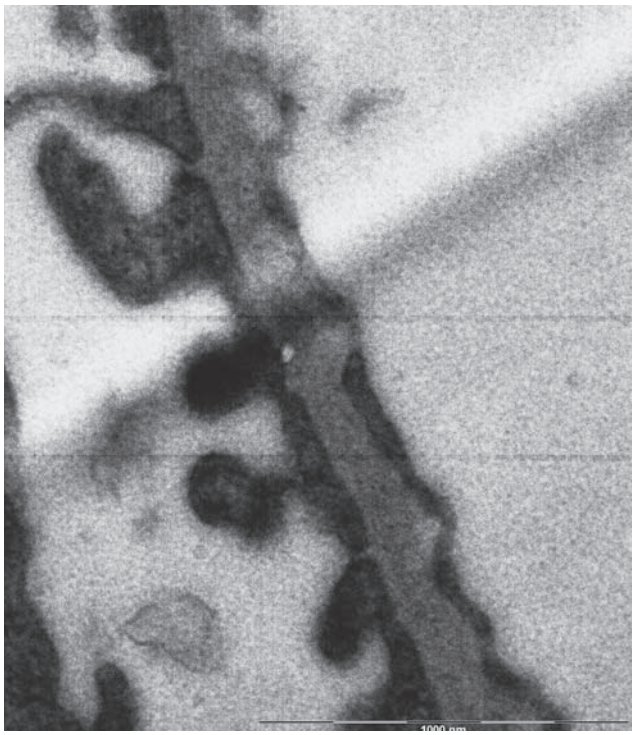

FIGURE 4. Case 2: lack of electron dense deposits at the capillaries; note the preserved pedicles (EM, X8000).

expression, localized masking of antigenic areas at Ig level, and early glomerular injury secondary to glomerular immune complexes (2,11,12). However, mutations in the C3 nephritic factor (C3NeF) and regulatory proteins in alternative complement pathway have recently been blamed in the pathogenesis (3,13).

The clinical presentation in i-C3-GN ranges from isolated microscopic or macroscopic hematuria to varying degrees of proteinuria plus hematuria (1,2,5). Some of the subjects might also present with nephrotic syndrome (1,2). Hypertension might be a complication of this disease. Yagi *et al*. have reported four pediatric i-C3-GN cases, two of which showed macroscopic hematuria and proteinuria with reduced glomerular filtration rate (GFR), one presenting with microscopic hematuria and proteinuria, and the remaining presenting with isolated microscopic hematuria. Therefore, the same authors have reported that none of the patients was hypertensive and serum total complement activity was normal, except for one case with persistent hypocomplementemia (decreased plasma C3) accompanied by circulating immune complexes that persisted over the next 10 years (14). In another study comparing patients with MPGN with isolated C3 deposition and C3-GN, the authors report that one out of 5 patients with C3-GN was a child presenting with decreased C3, C3NeF and decreased GFR, proteinuria plus hematuria (13). Similarly, our first case had macroscopic hematuria, severe proteinuria, hypertension and decreased GFR, whereas the other case had isolated macroscopic hematuria and non-nephrotic proteinuria. C3NeF levels could not be measured and genetic mutations of alternative complement pathway could not be examined in the patients due to normal C3 levels and rapid response to treatment.

The diagnosis of i-C3-GN is established relying on the demonstration of varying degrees of glomerular inflammation plus isolated subendothelial glomerular basal membrane and/or mesangial C3 deposition in kidney biopsy specimen, in the absence of underlying systemic disease (3). Biopsy findings also aid in differentiation of this disease from other forms of C3 glomerulopathy. For instance, subendothelial/mesangial electron dense deposits are observed in this disease, where a more intense and intramembraneous deposition is observed in dense deposit disease (DDD). Thickening of the glomerular capillary wall observed in MPGN is not seen in this disease (13). Our cases had nonspecific glomerular alterations in addition to isolated mesangial C3 deposition. We were directed to i-C3-GN since none of the patients had clinical and/or laboratory findings suggestive of autoimmune diseases including acute GN, systemic lupus erythematosus, febrile diseases including Henoch-Schönlein purpura, neoplastic diseases or sarcoidosis, Wegener's granulomatosis and polyarteritis nodosa.

The treatment of i-C3-GN and the relationship of this treatment with prognosis are not known. Previously, Grekas *et al*.

obtained good response to corticosteroid therapy in patients with minimal change i-C3-GN presenting with nephrotic syndrome; however, Ginesta *et al*. failed to obtain such a response in patients with similar clinicopathologic findings (1,2). Therefore, Yagi *et al*. administered combination therapy with cyclophosphamide, prednisolone, warfarin and ACE inhibitors for 6 months to two patients with moderate to severe mesangial proliferative GN since the response to steroid therapy is not known, and the above therapy led to remission of proteinuria and improvement of creatinine clearance. Additionally, a second renal biopsy performed in one of these patients to evaluate therapeutic efficacy of 6-month combined therapy showed significantly decreased mesangial cell proliferation. The authors examined another two patients with mild mesangial proliferative glomerulonephritis administered only ACE inhibitor and found good clinical course in these cases (14). We also administered cyclophosphamide for 3 months of the total of 6 months of combined therapy (prednisolone, cyclophosphamide, dipyridamole and ACE inhibitor) to the first patient presenting with nephritic-nephrotic syndrome, moderate mesangial proliferation in biopsy specimen and unresponsive to prednisolone therapy. All clinical and laboratory findings improved following this treatment and GFR increased from 75 mL/min/1.73 m^2 to 126 mL/min/1.73 m^2. The other patient with moderate mesangial proliferation and interstitial fibrosis with no marked proteinuria was administered ACE inhibitor therapy alone; proteinuria was observed to regress and one episode of macroscopic hematuria regressing without therapy was recorded.

It is not possible to determine for sure the prognosis and prognostic factors in i-C3-GN. Some authors have reported that impairment of renal function was not observed in any patients following prolonged follow-up (approximately 5.7 years), whereas other authors have reported patients progressing to end-stage renal disease (ESRD) over similar follow-up duration (2,15,16). Additionally, the same author has reported that severe mesangial proliferation, glomerular sclerosis and tubulointerstitial injury were observed in patients with ESRD, and severe proteinuria unresponsive to steroid therapy and hypertension might be prognostic in renal function impairment (2). The two cases presented in this manuscript had good prognosis despite having the previously mentioned factors of poor prognosis. This is supportive of the articles suggesting a good long-term prognosis in this disease.

Consequently, i-C3-GN is a rare disease of childhood, the exact pathogenesis, treatment and prognosis of which are not known. The degree of proteinuria and renal histologic findings are factors of poor prognosis in patients with chronic glomerulonephritis. However, proper treatment might affect long-term prognosis favorably in i-C3-GN patients with these risk factors.

REFERENCES

1. Grekas D, Morley AR, Wilkinson R, Kerr DNS. Isolated C3 deposition in patients without systemic diseases. Clin Nephrol. 1984;21:270-4.
2. Ginesta JC, Almirall J, Torras A, Darnell A, Revert L. Long-term evaluation of patients with isolated C3 mesangial glomerulonephritis. Clin Nephrol. 1995;43:221-5.
3. Fakhouri F, Fremeaux-Bacchi V, Noel LH, Cook HT, Pickering MC. C3 glomerulopathy: a new classification. Nat Rev Nephrol. 2010;6:494-9.
4. Larsen S. Immunofluorescent microscopy findings in minimal or no change disease and slight mesangioproliferative glomerulonephritis. Acta Pathol Microbiol Scand A. 1978;86:531.
5. Manno C, Proscia AR, Laraia E, Giangrande M, Di Carlo M, Salvatore C. Clinicopathological features in patients with isolated C3 mesangial proliferative glomerulonephritis. Nephrol Dial Transplant Suppl. 1990;1:78-80.
6. Kusumoto Y, Takebayashi S, Taguchi T, Harada T, Naito S. Long-term prognosis and prognostic indices of IgA nephropathy in juvenile and adult Japanese. Clin Nephrol. 1987;28:118-24.
7. Wyatt R, Kritchevsky S, Woodford S, et al. IgA nephropathy: longterm prognosis for pediatric patients. J Pediatr. 1995;127:913-9.
8. Hoggs R, Silva F, Wyatt R, Reisch J, Argyle J, Savino D. Prognostic indicators in children with IgA nephropathy – a report from the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol. 1994;8:15-20.
9. Gale DP, de Jorge EG, Cook HT, et al. Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis. Lancet. 2010;376:794-801.
10. Athanasiou Y, Voskarides K, Gale DP, et al. Familial C3 glomerulopathy associated with CFHR5 mutations: clinical characteristics of 91 patients in 16 pedigrees. Clin J Am Soc Nephrol. 2011;6:1436-46.
11. Shin ML, Gelfand MC, Nagle RB, Carlo JR, Green I, Frank MM. Localization of receptors for activated complement on visceral epithelial cells of the human renal glomerulus. J Immunol. 1977;118:869-73.
12. Doi T, Kanatsu K, Suehiro F, Nagai H, Yoshida H, Hamashima Y. Clinicopathological study of patients with mesangial isolated C3d deposition in various glomerular diseases. Nephron. 1987;46:188-93.
13. Servais A, Frémeaux-Bacchi V, Lequintrec M, et al. Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. J Med Genet. 2007;44:193-9.
14. Yagi K, Yanagida H, Sugimoto K, et al. Clinicopathologic features, outcome, and therapeutic interventions in four children with isolated C3 mesangial proliferative glomerulonephritis. Pediatr Nephrol. 2005;20:1273-8.
15. Dimitrova V, Minkova V, Belovezhdov N. Mesangial C3 glomerulonephritis. Vutr Boles. 1991;30:47-50.
16. Grcevska L, Polenakovic M. Long-term follow-up of patients with isolated C3 nephritis. Clin Nephrol. 1998;50:269-70.

SAŽETAK

C3 glomerulonefritis: dva pedijatrijska slučaja

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C3 glomerulopatija definira skupinu bolesti obilježenih odlaganjem samo C3 u glomerulima bez odlaganja imunoglobulina ili drugih proizvoda komplementa, a obuhvaća bolest gustih nakupina, membranoproliferativni glomerulonefritis tip 1 (MPGN), obiteljski tip 3 MPGN, obiteljski C3 glomerulonefritis udružen s mutacijom proteina 5 povezanog s faktorom H komplementa i idiopatski C3 glomerulonefritis. Nedavno je disregulacija sustava komplementa optužena za razvoj C3 glomerulonefritisa. Ovdje se prikazuju dva pedijatrijska slučaja vjerojatnog C3 glomerulonefritisa prema nalazima biopsije bubrega. U jednom slučaju zabilježen je nefrotsko-nefritični sindrom, a u drugom makroskopska hematurija, oba s dobrom prognozom.

Ključne riječi: glomerulonefritis, membranski; imunoglobulini; dojenče; dijete