A Clinicopathological Study of C1q Nephropathy at King Abdulaziz University

Ghadeer A Mokhtar, Sawsan M Jalalah

Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Keywords. C1q nephropathy, glomerulonephritis, child

Introduction. C1q nephropathy is a relatively rare idiopathic glomerulopathy characterized by mesangial immunoglobulin and complement deposits with dominance or co-dominance of C1q, with no evidence of systemic lupus erythematosus. We describe the incidence, clinical manifestation, histopathological features, and follow-up of patients with C1q nephropathy at our institute.
Materials and Methods. Of 750 kidney biopsy specimens obtained in the period of January 2000 to December 2011, all the cases that meet the criteria for the diagnosis of C1q nephropathy were retrieved. The histological slides were examined and the clinical charts were reviewed by 2 renal pathologists.
Results. We had 11 patients, all children, that met the criteria for the diagnosis of C1q nephropathy accounting for an incidence of 1.5%. The mean age at the time of presentation was 3.7 years and all the patients were presented with nephrotic syndrome. Two patients had microhematuria and 2 had hypertension. Histological examination of these cases showed variable degrees of mesangial cells hypercellularity and matrix expansion with focal segmental glomerulosclerosis observed in 2 cases. Nine patients were steroid resistant (82%) and 2 were steroid dependent. Six patients required immunosuppressive therapy and 1 patient developed end-stage renal disease.
Conclusions. In our series, C1q nephropathy affected predominantly young children. Mesangioproliferative pattern was the most frequent histopathological finding in these patients. Clinically, despite steroid resistance, the patients had a relatively good outcome; the worst prognostic outcome was associated with collapsing glomerulopathy.

IJKD 2015;9:279-85
www.ijkd.org

Original Paper

INTRODUCTION

C1q nephropathy is a relatively rare form of glomerulonephritis, characterized pathologically by dominant or co-dominant mesangial deposition of complement C1q, in the absence of clinical and serological evidence of systemic lupus erythematous.[1,2] With the increasing number of reported cases, it is emerging as an established independent disease entity. The disease manifests mainly in children and young adults with severe proteinuria and nephrotic syndrome that is resistant to steroid treatment with frequent relapses.[1] This study is the first series of C1q nephropathy cases in the western region of Saudi Arabia; the aim was to review the incidence, clinical features, and pathological findings of C1q nephropathy in cases presented at our institution and compare to previous reports from other centers in the world.

MATERIALS AND METHODS

Patients

In this retrospective study, 750 percutaneous

native renal biopsies between the periods of January 2000 to December 2011 were reviewed at our institution. All of the patients with the differential diagnosis of C1q nephropathy versus lupus nephritis were selected from the pathology archives. There were 11 cases that met the criteria for the diagnosis of C1q nephropathy described by Jenntte and later by D'Agati.[1] These criteria are: (1) the presence of dominant or co-dominant mesangial immunofluorescence staining for C1q; (2) corresponding mesangial electron-dense deposits by electron microscopy; and (3) negative antinuclear antibodies and absence of clinical evidence of systemic lupus erythematosus.

Pathology Examinations

The patients' charts were reviewed for the clinical presentation, laboratory findings, treatment and follow-up after obtaining the institution research ethics committee approval. The renal biopsies were reviewed by 2 renal pathologists with light microscopy, using (hematoxylin-eosin), periodic acid-Schiff, methenamine silver, and Masson trichrom stains; immunofluorescence studies, using Zeiss axiophot fluorescence microscope for the detection of immunoglobulins A, G, and M, and complements C1q, C3, and C4 (FITC conjugated polyclonal rabbit antihuman, Dako); and transmission electron microscopy (Philips CM100).

Definitions

Nephrotic syndrome was defined as proteinuria with 3.5 g/24 h of protein or greater. Nephrotic patients were classified according to their response to steroid as follows: steroid responsive, those who had complete remission of proteinuria during the treatment and the remission persisted for at least 2 months after stopping of the treatment; steroid dependent, where complete remission was obtained during the treatment but recurrence occurred when the dose was reduced below a critical level or relapse on 2 successive occasions; and steroid resistant, defined as no remission over a period of at least 4 consecutive weeks of steroid therapy. Remission was defined as a reduction in urine protein concentration to less than 0.15 g/24 h and reduction of erythrocytes to less than 3 cells per high-power field. Relapse was the reappearance of proteinuria on at least 3 consecutive examinations within 7 days. Hematuria was defined as 3 or more erythrocytes per high-power field of urinary sediment. The patient was regarded hypertensive if resting blood pressure was higher than the 90th percentile for age. Hypertension was defined as systolic or diastolic blood pressure above the 95th percentile for age, sex, and height. Renal insufficiency was defined by a calculated creatinine clearance below normal values for patient age and sex. Mesangial hypercellularity was defined as 4 or more mesangial cells per mesangial area. Interstitial inflammation and fibrosis and tubular atrophy were graded as mild (zero to 25%), moderate (> 25% to 50%), and severe (> 50%).

Statistical Analyses

The data were analyzed using the SPSS software program (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). Descriptive statistics of mean was used for continuous variables, and numbers (percentages) for categorical variables.

RESULTS

Clinical Features

We had 11 patients that meet the criteria for the diagnosis of C1q nephropathy through a review of 750 biopsies performed at our institution. All the patients were in the pediatric age group (6 girls and 5 boys). Their mean age at the time of presentation was 3.7 years and the median age was 2 years (range, 1.4 to 10 years). Six patients were Saudi and 5 were from other countries. Nine patients presented with steroid-resistant nephrotic syndrome (82%) and 2 patients with steroid-dependent nephrotic syndrome (18%). Microhematuria was observed in 2 patients. Blood pressure was elevated at the time of diagnosis in 2 patients. All the patients had normal kidney function at the time of presentation and all had negative antinuclear antibodies, hepatitis B surface antigen, and hepatitis C antibodies. Level of C3 was elevated in 2 patients, while C4 level was normal in all.

Two of the patients were sisters and their parents were second-degree cousins. Genetic screening in these two sisters confirmed the presence of the *NPHS1* gene mutation.

Follow-up data was available for 9 patients; the remaining 2 patients were referred only for renal biopsy but treated and followed up at different

hospitals. Eight patients had several admissions to hospital because of relapse of nephrotic syndrome. All of the patients were treated with oral methyelprednisolone. Three patients also started on oral cyclosporine for periods of 3 months, 2 years, and 4 years. Enalapril and furosemide were also given to all of the patients. One patient developed kidney failure 1 year after the diagnosis, complicated by heart failure, pleural effusion, and requiring several admissions to the intensive care unit, and started on hemodialysis and peritoneal dialysis. The remaining 8 patients had normal kidney function throughout the follow-up period. The two sisters continued to have a high proteinuria and low albumin level despite treatment, but other patients showed partial to complete response to therapy. Tables 1 and 2 summarize the clinical features of these 11 patients with C1q nephropathy.

Pathological Findings

Results for all cases are detailed in Table 3. On light microscopy, 6 cases showed segmental mesangial hypercellularity and mesangial matrix expansion (Figures 1 and 2). Two cases showed diffuse mesangial hypercellularity and matrix expansion. Mild mesangial matrix expansion was the only abnormality in 3 cases. Two cases showed additionally focal segmental glomerulosclerosis (FSGS), one of which was the collapsing variant and had severe interstitial fibrosis with moderate inflammation. Immunofluoresence study demonstrated dominant or co-dominant staining of C1q (Figure 3) in addition to other immunoglobulins, within the mesangial areas. In 3 cases a full-house reaction pattern of immunoglobulin and complement was detected. Ultrastructural examination revealed the presence of mesangial electron dense deposits in all the cases (Figure 4); in addition, rare subendothelial deposits were also present in 5 cases and subepithelial deposits in 4 cases. There were no tubuloreticular inclusions in endothelial cells in any of the cases.

DISCUSSION

C1q had been observed in the renal biopsy specimens in a wide range of renal disorders. It

Table 1. Clinical Data of Patients With C1q Nephropathy*

Patient	Age, y	Sex	Nationality	Clinical Presentation	Hematuria	Urine Protein	Serum Creatinine, μmol/L	Time Until Biopsy, mo	Treatment
1	2	Female	Pakistani	SRNS	No	4+	14	4	Methylprednisolone, Enalapril
2	1.4	Female	Yamani	SRNS	No	3+	18	3	Methylprednisolone, Cyclophosphamide, Cyclosporine, Enalapril, Losartan
3	1.9	Female	Yamani	SRNS	No	3+	23	2	Methylprednisolone, Cyclosporine, Enalapril
4	10	Male	Saudi	SDNS	No	4+	22	4	Data not available
5	2	Male	Pakistani	SRNS	No	3+	12	2	Methylprednisolone, Cyclophosphamide (oral), Enalapril, Furosemide
6	4	Female	Saudi	SRNS	Yes	3+	23	2	Methylprednisolone, Cyclophosphamide (oral), Furosemide, Enalapril
7	2	Male	Saudi	SDNS	Yes	4+	54	5	Methylprednisolone, Cyclophosphamide, Cyclosporine
8	5	Male	Saudi	SRNS	No	3+	56	9	Methylprednisolone, Furosemide, Labetalol, Amlodipine, Nifedipine
9	2	Female	Saudi	SRNS	No	3+	24	3	Methylprednisolone, Cyclophosphamide, Cyclosporine, Enalapril
10	3	Male	Somalian	SRNS	No	3+	18	4	Methylprednisolone, Furosemide, Enalapril
11	7	Female	Saudi	SRNS	No	4+	25	2	Data not available

*SRNS indicates steroid-resistant nephritic syndrome and SDNS, steroid dependent nephritic syndrome.

Table 2. Follow-up Data of 9 Patients With C1q Nephropathy*

Patient	Follow-up, y	Hospital Admissions	Serum Creatinine, μmol/L†	Urine Protein†	Current Treatment
1	5	0	20	Trace	Enalapril
2	12	5	69	5.69 g/24 h	Enalapril, Losartan, Furosemide, Ospen
3	6	2	10	4.5 g/24 h	Enalapril, Losartan, Furosemide, Captopril
4	…	…	…	…	…
5	2	2	20	2+	Prednisolone, Furosemide
6	2	1	45	0.51 g/24 h	Prednisolone, Enalapril
7	9	3	62	0.18 g/24 h	Cyclosporine, Prednisolone, Enalapril
8	2	5	56	4 g/24 h	Peritoneal Dialysis, Nifedipine, Furosemide, Atenalol
9	4	5	28	Negative	Prednisolone, Enalapril
10	1	2	30	2+	Prednisolone, Enalapril
11	…	…	…	…	…

*Ellipses indicate data were not available.
†Measurement on the last Follow-up visit.

Table 3. Pathological Features of 11 Patients With C1q Nephropathy

Patient	Light Microscopy	Immunofluorescence	Electron Microscopy
1	Focal segmental mesangial hypercelluarity and 1 glomerulus with focal segmental glomerulosclerosis	IgG (2+), C3 (1+), C1q (2+)	Large mesangial dense deposits and collapsed capillary loops
2	Mild mesangial matrix expansion	IgG (2+), IgA (2+), IgM (2+), C3 (2+), C4 (1+),C1q (3+)	Matrix expansion and mesangial and few subendothelial dense deposits
3	Mild mesangial matrix expansion	IgG (3+), IgA (2+), IgM (2+), C3 (2+), C4 (2+), C1q (3+)	Mild matrix expansion and small mesangial dense deposits
4	Diffuse mesangial matrix expansion and segmental mesangial hypercellularity	IgG (3+), IgA (3+), IgM (1+), C3 (3+), C4 (1+), C1q (3+)	Matrix expansion and mesangial dense deposits
5	Mild focal and segmental mesangial hypercellularity and matrix expansion	IgG (2+), IgM (1+), C3 (2+), C4 (1+), C1q (2+)	Matrix and cell increase Mesangial, subenodthelial, and rare subepithelial dense deposits
6	Diffuse mesangial cells and matrix increase and mild fibrosis	IgG (2+), IgA (3+), IgM (3+), C3 (3+), C4 (2+), C1q (3+)	Mesangial, subendothelial, and rare subepithelial dense deposits
7	Focal and segmental mesangial hypercellularity and matrix expansion	IgG (1+), IgA (2+), IgM (2+), C1q (2+), C3 negative, C4 negative	Mesangial dense deposits and rare collapsed loops
8	Segmental mesangial matrix expansion and cellularity, focal segmental glomerulosclerosis collapsing variant, severe interstitial fibrosis, and moderate inflammation	IgG (2+), IgA (trace), IgM (2+), C3 (2+), C1Q (2+), C4 trace	Mainly mesangial dense deposits, rare subendothelial and subepithelial, and collapsed segments
9	Segmental mesangial hypercellularity and matrix expansion and rare intracapillary neutrophils	IgG (2+), IgA (2+), IgM (+), C3 (1+), C1q (2+), mesangial cell	Mesangial cells and matrix increase and mesangial dense deposits
10	Focal segmental mesangial matrix expansion and hypercellularity	IgG (2+), IgM (1+), C3 (1+), C1q (2+), IgA negative, C4 negative	Mesangial and rare subepithelial and subendothelial dense deposits
11	Mild mesangial matrix expansion	IgG (2+), IgM (2+), C1q (2+)	Mesangial and rare subendothelial dense deposits

has been reported to be present in 50% of cases of membranoproliferative glomerulonephritis and also in biopsies from patients with lupus nephritis.[3,4] C1q is a complex protein that has a critical function in the activation of the classical complement pathway.[3,5]

C1q nephropathy was described as a distinct pathological entity first by Jennette and Hipp in 1985 who evaluated 800 renal biopsy specimens for immunostaining for C1q and found it to be positive in 36% of cases, including 15 patients with mesangial immune deposits and no serological or clinical evidence of systemic lupus erythematous and these patients were designated as having C1q nephropathy.[6] Thereafter, several case reports and case series have been published on C1q nephropathy by applying the criteria described by Jennette.[2,3,5,7-14]

The incidence of C1q is quite variable on different studies ranging from 0.2% to 2.5% in biopsies from children and adult to up 16.5% among renal biopsies

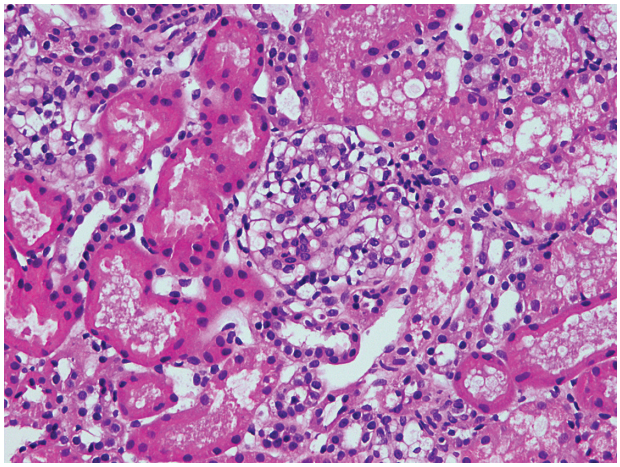

Figure 1. A glomerulus showing mild increase in the mesangial cellularity (hematoxylin-eosin, × 200).

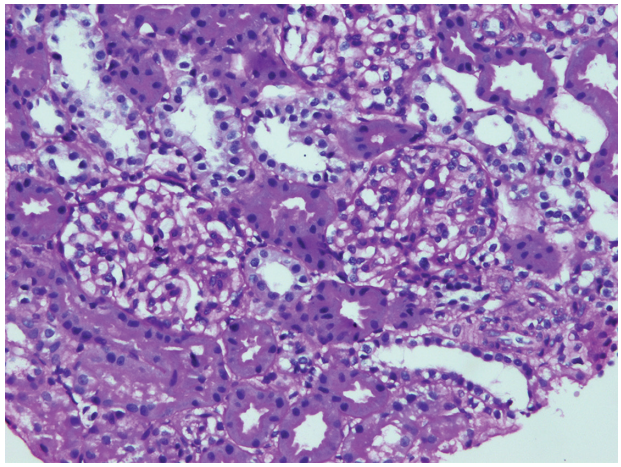

Figure 2. Two glomeruli showing expansion of mesangial matrix and segmental mesangial cells hypercellularity (periodic acid-Schiff, × 200).

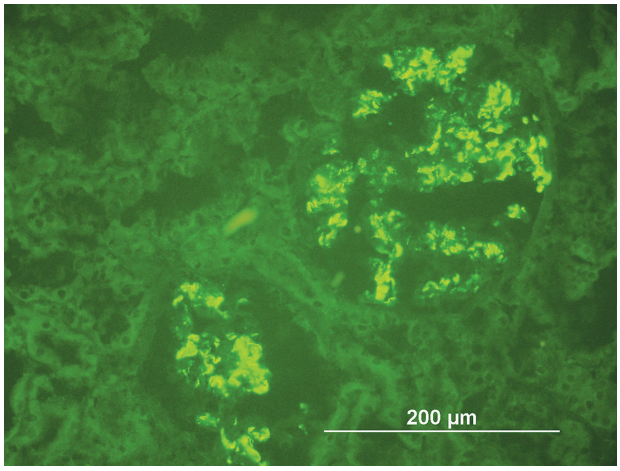

Figure 3. Immunofluorescence micrograph of 2 glomeruli demonstrating positive mesangial staining for C1q (direct immunofluorescence, × 250).

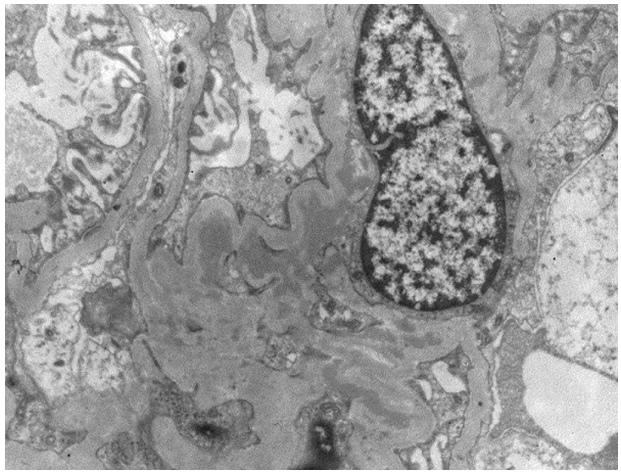

Figure 4. Transmission electron micrography showing large mesangial dense deposit (uranyl acetate and lead citrate; TV4).

in children with persistent nephrotic syndrome.[2,11] The most recent report by Roberti and colleagues had a cumulative incidence of C1q nephropathy of 5%.[7] In the current study C1q nephropathy constituted 1.5% of all native renal biopsies over a period of 11 years. This marked variation in the incidence of C1q nephropathy between studies could be attributed to the difference in the age of patients included in various studies and the different practice of each laboratory including the routine use of C1q staining as a part of immunofluorescence analysis and the interpretation of the staining intensity.

C1q nephropathy has been reported to be a disease of older children and young adults with an average age of 17.8 years and an almost equal sex distribution.[2,3,5-7] This is slightly different from our patients population who were younger with a mean age of 3.7 years. For all the published pediatric C1qnephropathy series, the mean age at presentation was 9.6 years.[3] However, our age distribution is very similar to the result obtained by Wong and colleagues who described 9 children with minimal change nephrotic syndrome and mesangial C1q deposition.[14] These children had a median age of 2.7 years at diagnosis (range, 1.3 to 15 years). Two of our patients were younger than 2 years. Presentation at this very young age has been rarely reported in a 10-month-old infant,[10] a 15-month-old,[12] and a 1-month-old who presented with congenital nephrotic syndrome.[15]

C1q nephropathy usually presents with nephrotic-range proteinuria that has a poor

response to steroids.[2,3,5-7,10-13] It also has been reported to cause non-nephrotic range proteinuria associated with microhematuria, hypertension or renal insufficiency in children.[2,11,12] Nishida and colleagues described 4 cases of C1q nephropathy in children; 3 of them had asymptomatic urine abnormalities and a relatively good clinical course.[9] Secondary C1q nephropathy has been reported in patients with viral infection or rarely rheumatoid arthritis.[11] Similar to most of the studies, all of our patients presented with nephrotic syndrome, 9 were resistant to steroid and 2 were dependent; in addition, 2 patients presented with microhematuria and hypertension.

Interestingly in this current study, 2 of the patients were sisters who had genetic mutation of the *NPHS1* gene. C1q nephropathy has been reported in association with Gitelman syndrome, Bartter syndrome, chromosome 13 deletion, and severe atopic dermatitis.[17] These associations could be explained by genetic predisposition; however, no molecular testing has been performed in these studies to prove it. These 2 young sisters with C1q nephropathy had been reported by Kari and Jalalah in a previous study.[17] However, at the time of their report publication, the genetic tests results were not available. Thereafter, no other familial or hereditary cases of C1q nephropathy have been reported so far.

The histological pattern of glomerular disease seen by light microscopy with C1q are diverse but in recent studies of 20 cases of C1q nephropathy by Lau and colleagues[10] and 12 cases by Kersnik and associates,[2] they had FSGS pattern seen in 40% to 50%, minimal change disease pattern in 30%, and proliferative glomerulonephritis in 15% to 17% of cases. A more recent cohort of 82 patients with C1q nephropathy described minimal change disease in 27(38%), FSGS pattern in 11(16%) and proliferative glomerulonephritis in 20 (28%).[13] Many studies have confirmed the presence of electron-dense deposits in almost all the renal biopsy samples including mesangial, paramesangial, and subendothelial areas.[2,11,13] Our present study demonstrated that the predominant pathological finding was the mesangioproliferative pattern with mesangial dense deposits in all the cases. In addition, FSGS was noted in 2 cases; one of these 2 cases showed a collapsing glomerulopathy pattern with collapsed capillary loops and hypertrophied podocytes. The association of collapsing FSGS with C1q nephropathy has been reported in 2 studies. Markowitz and colleagues studied 19 patients with C1q nephropathy, of which 6 cases showed collapsing FSGS pattern.[18] Recently, Reeves-Daniel and colleagues reported 2 cases of C1q nephropathy in African-Americans with the morphological features of C1q nephropathy that rapidly progressed to end-stage renal disease.[19]

The prognosis of patients with C1q nephropathy depends largely on the clinical manifestation of the disease and the underlying histopathological findings.[2] Patients with minimal change disease or other patterns of glomerular disease have more favorable outcome according to several studies,[2,10,13] while patients with nephrotic syndrome and FSGS have a less favorable prognosis.[2,3,5,13] Patients with nephrotic syndrome and minimal change disease had much more typical response with steroid treatment, but frequent relapses up to 66% may occur according to study of 12 patients by Fukuma and colleagues[12] and Wong and coworkers[14] with the requirement of immunosuppressive therapy to control the relapse. Nearly two-thirds of pediatric patients with C1q nephropathy were steroid resistant and 30% progressed to end-stage renal disease.[3]

In our study, 9 of the patients were steroid resistant and 2 were steroid dependent. In addition, 6 of the 9 steroid-resistant patients required additional immunosuppressive therapy with cyclophosphamide and cyclosporine. Of the 9 patients in whom clinical follow-up was available, only 1 patient developed end-stage renal disease 1 year after the diagnosis and this patient had a collapsing glomerulopathy pattern in the renal biopsy.

CONCLUSIONS

We described our experience with C1q nephropathy; the patient population was predominately in pediatric age group at presentation. The most dominant histopathological finding in these patients was mesangioproliferative pattern. Despite steroid resistance, patients had a relatively good outcome; the worst prognostic outcome was associated with collapsing glomerulopathy. However, this study is limited by the small number of patients studied. Future multicenter study of C1q nephropathy in this part of the world is highly

required to better understand the disease with regard to pathogenesis and prognostic predictors and to define the optimal therapy and predict the long-term outcome.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Mii A, Shimizu A, Masuda Y, et al. Current status and issues of C1q nephropathy. Clin Exp Nephrol. 2009;13:263-74.
2. Kersnik Levart T, Kenda RB, Avgustin Cavić M, Ferluga D, Hvala A, Vizjak A. C1Qnephropathy in children. Pediatr Nephrol.2005;20:1756-61.
3. Wenderfer SE, Swinford RD, Braun MC. C1q nephropathy in the pediatric population: pathology and pathogenesis. Pediatr Nephrol. 2010;25:1385-96.
4. Turnberg D, Cook HT. Complement and glomerulonephritis: newinsights.Curr Opin Nephrol Hypertens. 2005;14:223-8.
5. Gunasekara VN, Sebire NJ, Tullus K. C1q nephropathy in children: clinical characteristics and outcome. Pediatr Nephrol. 2014 ;29:407-13.
6. Jennette JC, Hipp CG. C1q nephropathy: a distinct pathologic entity usually causing nephrotic syndrome. Am J Kidney Dis. 1985;6:103-110.
7. Roberti I, Baqi N, Vyas S, Kim DU. A single-center study of C1q nephropathy in children. Pediatr Nephrol. 2009;24:77-82.
8. Srivastava T, Chadha V, Taboada EM, Alon U. C1q nephropathy presenting as rapidly progressive crescentic glomerulonephritis. Pediatr Nephrol. 2000;14:976-9.
9. Nishida M, Kawakatsu H, Komatsu H, Ishiwari K, Tamai M, Sawada T. Spontaneous improvement in a case of C1qNephropathy. Am J Kidney Dis. 2000;35:1-6.
10. Lau KK, Gaber LW, Delos Santos NM, Wyatt RJ .C1q nephropathy: features at presentation and outcome. Pediatr Nephrol. 2005;20:744-9.
11. Malleshappa P, Vankalakunti M. Diverse clinical and histology presentation in C1q nephropathy. Nephro-urol Mon. 2013;5:787-91.
12. Fukuma Y, Hisano S, Segawa Y et all. Clinicopathologic correlation of C1q nephropathy in children. Am J Kidney Dis. 2006; 47(3):412-8.
13. Vizjak A, Ferluga D, Rozic M, et al. Pathology, clinical presentations, and outcomes of C1q nephropathy. J Am Soc Nephrol. 2008;19:2237-44.
14. Wong CS, Fink CA, Baechle J, Harris AA, Staples AO, Brandt JR. C1q nephropathy and minimal change nephrotic syndrome. Pediatr Nephrol. 2009;24:761-7.
15. Kuwano M, Ito Y, Amamoto Y, Aida K. A case of congenital nephrotic syndrome associated with positive C1q immunofluorescence. Pediatr Nephrol. 1993;7:452-4.
16. Nishida M, Kawakatsu H, Okumura Y, Hamaoka K. C1q nephropathy with asymptomatic urine abnormalities. Pediatr Nephrol. 2005;20:1669-70.
17. Kari JA, Jalalah SM. C1q nephropathy in two young sisters. Pediatr Nephrol. 2008;23:487-90.
18. Markowitz GS, Schwimmer JA, Stokes MB, et al. C1q nephropathy: A Variant of focal segmental glomerulosclerosis. Kidney Int. 2003;64:1232-40.
19. Reeves-Daniel AM, Iskandar SS, Bowden DW, et al. Is collapsing C1q nephropathy another MYH-9-associated kidney disease? A case report. Am J Kidney disease. 2010;55:21-4.

Correspondence to:
Ghadeer A Mokhtar, MBBC, FRCPC
Department of Pathology, Faculty of Medicine, King Abdulaziz University
PO Box: 80215, Jeddah 21589, Saudi Arabia
Tel: +966 5053 52367
E-mail: ghadeer200@hotmail.com

Received July 2014
Revised March 2015
Accepted April 2015