Collapsing glomerulopathy, the Saudi Arabian scenario

A study of 31 cases and a review of literature

Sufia Husain, *MD, FRCPath.*

ABSTRACT

الأهداف: مقارنة الظواهر السريرية المرضية لهذا الاعتلال بمستشفى رعاية ثالثية في المملكة العربية السعودية مع الأدبيات العالمية.

الطريقة: في دراسة استرجاعية، تم تحديد وتحليل جميع الحالات التي تم تشخيصها من الاعتلال الكبيبي الشديد خلال الفترة من 2004–2015 م . وتم مراجعة ومقارنة النتائج السريرية المرضية جنبًا إلى جنب مع الشواهد الإنذارية ومقارنتها مع الأدبيات الموثقة.

النتائج: تم تحديد ما مجموعه 31 مريض بالاعتلال الكبيبي الشديد، وكانت غالبيتهم من الذكور البالغين. وكانت جميع حالات الاعتلال الكبيبي الشديد لدينا مجهولة السبب. وكان جميع المرضى من العرب، غير المصابين بفيروس نقص المناعة البشرية، ولم يكن أيٌّ منهم من أصل أفريقي أو أعطى تاريخًا لتعاطي المخدرات. تراوح عدد الكبيبات المصابة بشدة في كل خزعة من 1 إلى 9 . وقد لوحظت أيضًا أنواع أخرى من الإصابة بالاعتلال الكبيبي القطعي المركزي مثل المحيطة بالنقير أو غير المحددة سلفًا (NOS and Perihilar). كان هناك طمس واسع النطاق للخلايا الرجلاء. ومع العلاج، لوحظ وجود هَدْأة وتعافٍ (كامل/جزئي) في نصف المرضى تقريبًا. نحو ربع المرضى لم يستجيبوا للعلاج. والربع الآخر ازدادت حالته سوءًا ووصل إلى مرحلة النهاية من اعتلال الكلى (ESKD)، وكان متوسط الوقت اللازم للوصول إلى مرحلة النهاية من اعتلال الكلى منذ وقت تشخيص الخزعة نحو 23 شهرًا.

الخاتمة: العلاقة بين النتائج السريرية المرضية والشواهد الإنذارية لحالات اعتلال كبيبات الكلى الشديد المشخصة لدينا في المستشفى كانت مشابهة لما في الأدبيات العالمية. يجب فحص جميع المرضى باعتلال كبيبات الكلى الشديد للكشف عن أي من المسببات الكامنة. هناك حاجة إلى مزيد من الأبحاث لدراسة الفسيولوجيا المرضية وتحسين طرق العلاج.

Objectives: To compare the clinico-pathological features of collapsing glomerulopathy (CG) at a tertiary hospital in Saudi Arabia with the world literature.

Methods: In a retrospective study, all biopsy-diagnosed cases of CG between 2004-2015 were identified and analyzed, at King Khalid University Hospital, King Saud University, Riyadh. The clinico-pathological findings along with prognosis were reviewed and compared with the reported literature.

Results: Thirty-one CG patients were identified, most were adult males. All the CG cases were idiopathic, all Arabs, none HIV positive, none of African descent, and none with a history of drug abuse. The number of glomeruli with collapsing lesions per biopsy ranged from 1 to 9. Other types of FSGS lesions (not otherwise specified and perihilar) were also noted. There was extensive podocyte effacement. Upon treatment, remission (complete/partial) was noted in almost half the patients; around one fourth did not respond to treatment; and one fourth progressed to end stage kidney disease (ESKD). The median time taken to develop ESKD from the time of biopsy diagnosis was 23 months.

Conclusion: The clinico-pathological and prognostic correlates of CG in Saudi Arabia are comparable with that of the world literature. The management protocol at our center is the same as that practiced in different parts of the world, and the prognosis is overall poor.

Saudi Med J 2017; Vol. 38 (5): 509-516
doi: 10.15537/smj.2017.5.19299

From the Department of Pathology and Laboratory Medicine, College of Medicine, King Khalid University Hospital Medical City, King Saud University, Riyadh, Kingdom of Saudi Arabia.

Received 8th October 2016. Accepted 2nd February 2017.

Address correspondence and reprint request to: Dr. Sufia Husain, Assistant Professor, Department of Pathology and Laboratory Medicine, College of Medicine, King Khalid University Hospital Medical City, King Saud University, Riyadh, Kingdom of Saudi Arabia. E-mail: sufiahusain@hotmail.com
ORCID ID: orcid.org/0000-0003-3486-9356

Collapsing glomerulopathy (CG) is an aggressive variant of focal and segmental glomerulosclerosis (FSGS).[1] It was first described in the literature in 1986.[2] It typically presents with significantly high levels of nephrotic range proteinuria refractory to standard therapeutic protocols and progressive renal failure. On light microscopy, the affected glomeruli show either segmental or global glomerular tuft collapse with wrinkling of the glomerular basement membrane (GBM) and hyperplasia and hypertrophy of the epithelial cells that overlie the collapsed tuft, in the urinary space. Tubulointerstitial injury is also an important component of this disease, which is displayed in the form of cystically dilated and atrophic tubules, interstitial inflammation and interstitial fibrosis. Immunofluorescence (IF) is negative for IgA, IgG, and C1q. There may be focal, trace to mild non-specific staining with IgM and C3 in the collapsed areas. On electron microscopy (EM), commonly there is extensive to diffuse effacement of the epithelial cell foot processes/podocytes and the areas of collapse show wrinkling of the GBM and proliferation of the overlying epithelial cells. Electron dense immune deposits are not seen.

Collapsing glomerulopathy is often associated with human immunodeficiency virus (HIV) and African race. It exhibits a relatively more rapid progression to end stage kidney disease (ESKD), as compared with the other subtypes of FSGS.[1] As awareness of CG is growing, it is being increasingly diagnosed globally including in the Middle Eastern countries. In Saudi Arabia, the incidence of CG is on the rise due to the growing understanding of this entity among pathologists and nephrologists. There is very limited documented literature on CG in Saudi Arabia. This article presents a retrospective clinico-pathological study of all the cases of the collapsing variant of FSGS diagnosed at a tertiary level hospital in Saudi Arabia, between the year 2004 and 2015. The objective of this study is to assess the clinical and histological presentation of CG from a different geographic perspective. The clinical presentation, disease course, biopsy findings with the various histological parameters, therapeutic regimen, and the outcome are assessed for each patient in this research. An updated review of the literature is also conducted.

Disclosure. The author had no conflict of interests, and the work was not supported or funded by any drug company.

Methods. This retrospective study was conducted at King Khalid University Hospital, King Saud University, Riyadh, in accordance to, and with the ethical approval of the Institutional Review Board and as per the principles of the Helsinki Declaration. All the native or allograft renal biopsy cases diagnosed with FSGS from January 2004 to December 2015 were re-examined and classified according to Columbia classification.[1] Light microscopy slides stained with hematoxylin and eosin, Periodic acid-Schiff, Jones silver, Masson trichrome, and Congo red were reviewed. The digital images of the EM study were also retrieved and re-evaluated. The IF findings (IgA, IgG, IgM, C3, C1q, kappa, lambda, fibrinogen and albumin) obtained from the reports were correlated in each case. Only cases that fulfilled the minimum diagnostic criteria for the collapsing variant of FSGS in accordance with the Columbia classification, were included in this study and they are: the presence of at least one glomerulus with segmental/global collapse with wrinkling and obliteration of the affected glomerular tuft along with hypertrophy and hyperplasia of overlying epithelial cells.[1] Based on this criteria, all the cases of collapsing FSGS were identified. Patients with a history of any other additional or concurrent renal disease were excluded from this study. The relevant patient data, clinical presentation, laboratory and biopsy findings, treatment and course of the disease for each CG patient were obtained from the medical records. In addition, the serum creatinine levels at the time of biopsy, from the most recent follow up, or at study conclusion were compared. Each patient around the time of biopsy was investigated and serologically tested for human HIV infection, hepatitis B and C infection (HBV and HCV), anti-nuclear antibody titer, and serum complements. Also, if clinically suspected, tests for Parvovirus B19 and anti-neutrophilic cytoplasmic antibody were performed. Each biopsy was evaluated for the following histopathological variables: the total number of glomeruli identified, number of glomeruli with global sclerosis, number of glomeruli with collapse (global or segmental), the extent of overlying epithelial hyperplasia and hypertrophy, presence of any other type of segmental lesion, presence of cystically dilated tubules, tubular atrophy, interstitial fibrosis, and vascular changes. Additionally, wherever appropriate, a

semi quantitative scoring system was applied, from 0 to 3 in which: 0 = absent/negative, 1 (mild) = up to 25% of affected, 2 (moderate) = 26% to 50% affected, 3 (severe) = more than 50% affected.

Nephrotic range proteinuria was defined as proteinuria of ≥3.5 g/day. Steroid resistant nephrotic syndrome was defined as no remission after 4 weeks of regular and adequate steroid therapy. Remission was defined as either complete (trace or no proteinuria of ≤0.3 g/day with a stable renal function) or partial (50% reduction from peak proteinuria value with less than <3.5 g/day and stable renal function). The ESKD was defined as the point where renal replacement therapy (dialysis) was started.

Data analysis from Microsoft excel was used for statistical studies.

Results. From January 2004 to December 2015, a total 201 FSGS biopsies were identified, out of which 36 (18%) biopsies from 31 (15%) patients (3 patients had more than one biopsy) fulfilled the criteria according to the Columbia classification of FSGS, for CG.

Demographic findings. All patients were Saudis of Arab descent, and none were of African origin. The age range at the time of biopsy diagnosis was broad and varied from 2 to 95 years old, with an average age of 28, and a median age of 21. Eight patients (26%) were in the pediatric and adolescent age group ranging between 2 and 17 years. The remaining 23 patients were adults ranging from 19 to 95 years of age (74%). There were 20 (65%) males and 11 (35%) females, with a male to female ratio of 1.8:1.

Clinical and laboratory findings are summarized in **Table 1**. All patients presented with nephrotic range proteinuria at the time of biopsy, with an exception of one who had sub-nephrotic range proteinuria. Six (19%) patients also had hypertension; 8 (26%) had microscopic hematuria: and 7 (23%) had both hypertension and hematuria. The serum creatinine level of each patient was within normal limits at the time of biopsy except one patient who exhibited the features of ESKD with a hypertensive crisis and high serum creatinine level. The serum creatinine and the proteinuria at the time of biopsy, did not correlate with the number of collapsing lesions and the clinical outcome. All our patients tested negative for HIV, HBV, HCV, and Parvovirus B19 infection. The anti-nuclear antibody and anti-neutrophilic cytoplasmic antibody were negative in all. None gave a history of recreational IV drug abuse, bisphosphonate drug therapy, interferon treatment, or any hematological malignancy, or dyscrasias.

Kidney biopsy findings are shown in **Table 2**, and **Figures 1 & 2**. A median of 21 glomeruli with 2 globally sclerosed glomeruli were noted per biopsy. A median of 2 glomerular collapsing lesions was identified per

Table 1 - Clinical and laboratory findings of 31 patients.

Clinical variables	n (%)
Age range	2-95 years old (median: 21 years old)
Children and adolescent	9 (26)
Adults	23 (74)
Male	20 (65)
Female	11 (35)
African race	0
Human immunodeficiency virus infection	0
Intravenous drug abuse	0
Nephrotic range proteinuria	30 (97)
Hematuria	15 (48)

Table 2 - Kidney biopsy findings of 31 patients.

Biopsy variables	Biopsies (n=36 for histology and immunoflouresence, n=31 for electron microscopy)
Median number of glomeruli per biopsy	21
Median number of global glomerular sclerosis per biopsy	2
Median number collapsed glomeruli per biopsy	2 (ranging from 1 to 9)
Hyperplasia and hypertrophy of the epithelial cells overlying the collapsed tuft	
Mild	22 (61)
Prominent	14 (39)
Cystically dilated tubules	21 (58)
Interstitial fibrosis and tubular atrophy	
Mild	22 (61)
Moderate	8 (22)
Severe	6 (17)
Immunoflourescence	Negative for IgA, IgG, C3 and C1q in all biopsies
Podocyte effacement on electron microscopy	
Diffuse	18 (58)
Extensive but no diffuse	11 (35)
Focal	2 (7)
Electron dense immune deposits on electron microscopy	0
Tubulorecticular inclusions on electron microscopy	0

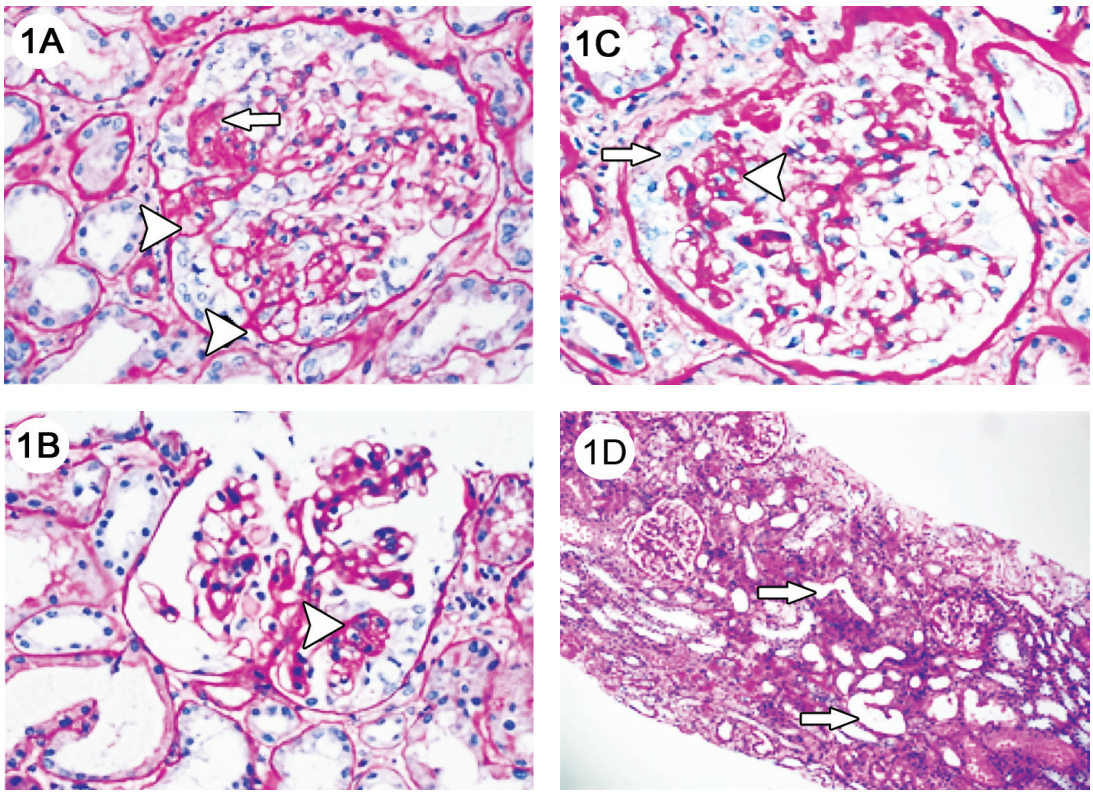

Figure 1 - Light microscopy photomicrograph of a **A)** renal biopsy in a case of collapsing glomerulopathy shows segmental collapse of the glomerular tuft (arrow) with hyperplasia and hypertrophy of the overlying epithelial cells. Another tuft showing NOS (not otherwise specified) type of segmental sclerosis with adhesion to the Bowman's capsule is also noted (arrowhead). (Periodic Acid Schiff stain; original magnification x400.) **B)** renal biopsy in a case of collapsing glomerulopathy, shows a small focus of segmental collapse of the glomerular tuft (arrowhead) with mild hyperplasia of the overlying epithelial cells. (Periodic Acid Schiff stain; original magnification x400.) **C)** renal biopsy in another case of collapsing glomerulopathy, shows segmental glomerular tuft collapse (arrowhead) with mild hyperplasia of the overlying epithelial cells (arrow) and some resorption protein droplets. (Periodic Acid Schiff stain; original magnification x400.) **D)** renal biopsy in a case of collapsing glomerulopathy, shows several cystically dilated tubules (arrows). The intervening glomeruli in this image show mild glomerulomegaly. (Periodic Acid Schiff stain; original magnification x100.)

biopsy (mean: 3 and range: 1 to 9 collapsing lesions). All biopsies showed hyperplasia of the overlying epithelial cells and the hyperplasia was prominent in around 40% of the CG biopsies. In addition to collapsing lesions, other types of segmental lesions were also noted in 61% of the biopsies, they were not otherwise specified (NOS) type of sclerosis (44% of the biopsies), perihilar sclerosis (14% of the biopsies), and a combination of both perihilar and NOS lesions (3% of the biopsies). The remaining 39% of the biopsies showed only collapsing lesions. The serum creatinine levels and the proteinuria, at the time of biopsy, did not correlate with the number of collapsing lesions. Cystic dilatation of the renal tubules was noted in 58% of the biopsies. Interstitial fibrosis and tubular atrophy varied from mild in 61%, moderate in 22%, and severe in 17% of the biopsies. Intimal fibrosis of the interlobular arteries ranged from: absent in 36%, mild in 36%, and moderate in 28% of biopsies. On IF, all the biopsies were completely negative for IgA, IgG, C3, C1q, and fibrinogen. However, some of the cases showed focal and segmental granular positivity with IgM in the glomerular sclerotic or collapsed areas. All biopsies showed mild to moderate staining with resorption protein albumin in the renal tubules. There was no availability of EM images for 5 biopsies. In the biopsies where EM images were available, the epithelial cell foot processes displayed diffuse effacement in 58%, extensive but not diffuse effacement in 35%, and focal effacement in 7%. Wrinkling of the GBM was present in the collapsed segments with overlying podocyte hyperplasia. No electron dense immune deposits or tubuloreticular inclusions were noted.

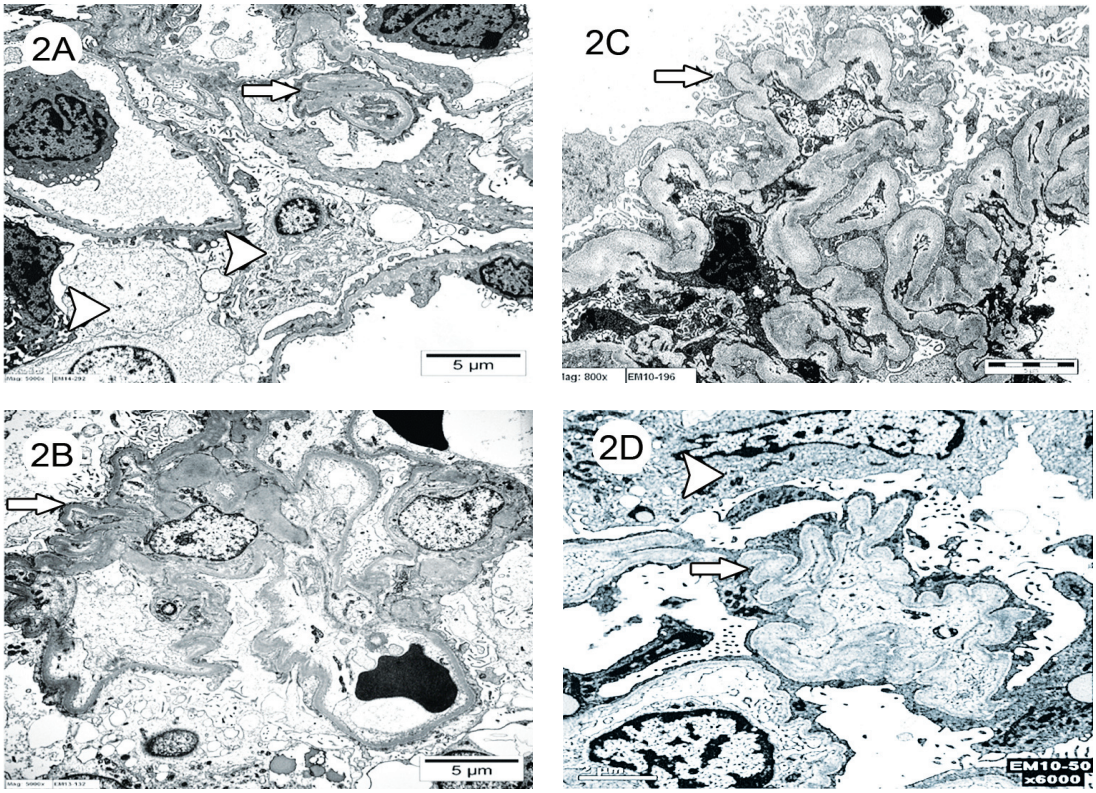

Figure 2 - Electron micrographs from renal biopsies diagnosed with collapsing glomerulopathy are shown. All the images exhibit different degrees of collapse in the capillary loops (arrows) with diffuse effacement of the epithelial cell foot processes and microvilli formation. Hypertrophy of the epithelial cell (arrowheads) is also seen in images (Uranyl acetate and lead citrate; original magnification **A)** x5000, **B)** x5000, **C)** x800 and **D)** x6000)

Treatment and clinical follow up at study conclusion. Patient management included control of proteinuria, blood pressure, dyslipidemia (if present), and salt restriction. The optimal management protocol followed in our hospital for CG patients include steroids, intravenous (IV) cyclophosphamide infusion, mycophenolate mofetil, and angiotensin converting enzymes. Patients who presented with rapidly progressive renal failure were given IV pulse methylprednisolone 250-500 mg for 3 days followed by oral prednisolone. Patients with stable glomerular filtration rate were started on oral prednisolone 1mg/kg body weight/day for 4-8 weeks followed by tapering of prednisolone by 5 mg every week until maintenance of 5 mg/day for the next 12 months. None of the patients went into remission under standard prednisolone therapy. All our patients were steroid resistant, except one, a 14-year-old male who was partially steroid responsive. The cyclophosphamide was administered as an IV infusion 750 mg/square meter of body surface area monthly for 3 to 6 months. After 6 doses of IV Cyclophosphamide, patients were switched to oral mycophenolate mofetil (Cellcept) 2 gm/day for the next 2 years. Follow up data showed variable response to treatment. Out of the 31 patients in this study, 8 (26%) went into complete, and 6 (19%) into partial remission; 7 (23%) did not show any significant response to treatment; 8 (26%) patients progressed to ESKD from CG, out of which one underwent renal transplant and is currently stable with no proteinuria, whereas others are on dialysis, awaiting renal transplant; one patient already had features of ESKD at the time of biopsy diagnosis; and lastly, one patient with recurrent CG in allograft kidney also developed transplant glomerulopathy. The time taken to develop ESKD from the time of biopsy diagnosis ranged from 6 months to 126 months with a median of 23 months.

Discussion. Collapsing glomerulopathy is a distinct, and aggressive clinicopathological variant of

FSGS.[3] It is a biopsy diagnosis, defined by the presence of at least one collapsing lesion in at least in one glomerulus associated with hyperplasia and hypertrophy of the overlying epithelial cells. It is usually associated with severe tubulointerstitial disease. The term CG was first used in 1986.[2] It is mainly seen in adults with a male predominance, but is well documented in the pediatric population as well.[4,5] Initially, it was thought to be a disease of the African race and of persons infected with HIV and/or IV drug users and hence, considered to be a part of the HIV-associated nephropathy.[6,7] In 1994, Detwiler et al[8] reported idiopathic collapsing FSGS in the absence of HIV infection and IV drug use.[8] Laurinavicius et al,[9] also demonstrated CG in non-black, non-HIV infected, and non-IV drug users. Our patients too are non-black, non-HIV infected, and non-IV drug users.

In the current study, 18% of the biopsies diagnosed as FSGS were classified as the collapsing variant. Our data is concordant with the world literature in which the incidence of CG ranges from 6-24% of idiopathic FSGS biopsies.[10-12] Collapsing glomerulopathy typically presents as steroid resistant nephrotic syndrome with varying degrees of renal dysfunction such that it usually exhibits rapid progression to renal failure when compared with the other variants of FSGS.[1] All our cases, except one (which was steroid responsive) presented with steroid resistant nephrotic syndrome. Collapsing glomerulopathy can recur in an allograft kidney after a renal transplant or arise de novo. Morphologically, the biopsy findings in our study are similar to those documented in the literature: effacement of the epithelial cell foot processes, collapse and retraction of glomerular capillary tufts, hyperplasia and hypertrophy of the adjacent epithelial cells with the formation of pseudo-crescents, and microcytic changes of the renal tubules.[1] On light microscopy, the hyperplasia and hypertrophy of the epithelial cells appear like a pseudo crescent and it may mimic crescentric glomerulonephritis, but the clinical presentation along with the IF and EM findings should be able to easily distinguish CG from glomerulonephritis with crescents. The epithelial hyperplasia and hypertrophy can also be seen in cellular FSGS, though the segmental lesion is endocapillary proliferation, which is in contrast to the collapsing tuft of CG.

The etiology for this collapsing pattern of glomerular injury is wide and varied. It can be idiopathic, reactive/ secondary to a prior disease condition, and occasionally genetic. Idiopathic disease is the most common type. The reactive type of CG can be secondary to various infections, drugs, autoimmune conditions, and rarely malignancies. The most common infection implicated in CG is HIV infection, and others include cytomegalovirus, parvovirus B19, HCV, and human T cell lymphotrophic virus.[9,13,14] Autoimmune disorders like systemic lupus nephritis has also shown collapsing glomerular lesions.[15,16] Neoplastic conditions like hemophagocytosis syndrome and multiple myeloma, drugs like interferon-α and bisphosphonates (pamidronate) can also lead to CG.[17-20] Collapsing glomerulopathy has also been reported as de novo disease post renal transplant.[21,22] Occasional genetic/ familial forms have been reported.[23] It has been postulated that the human Apolipoprotein L1 encoded by APOL1 gene, seen in the African race, is associated with FSGS and HIV-associated nephropathy, and is therefore probably associated with idiopathic CG as well.[24,25] Nichols et al[26] in a recent article reported a cohort of high-risk APOL1 genotype patients with viral infection, who on receiving interferon therapy developed CG. They illustrated that interferon upregulation induced APOL1 expression leading to APOL1 and interferon associated CG. Other genes implicated include the mitochondrial genes expressing coenzyme Q2.[27] No genetic studies were carried out on our patients especially in regards to APOL1 status, since it may be an underlying risk factor. Genetic studies on this cohort maybe performed in the future. Otherwise, none of our patients had any of the above-mentioned etiological conditions. All cases in this study group were therefore classified as idiopathic CG.

The current theory in the pathogenesis of CG is that, there is an apoptotic or necrotic insult to the glomerular and tubular epithelial cells by either an intrinsic or extrinsic injurious agent. This leads to mitochondrial dysfunction, podocyte injury, and podocyte loss, which leads to the activation and aberrant proliferation of the parietal epithelial cells of the Bowman capsule, forming pseudo crescents in the glomeruli.[28] Initially, it was believed that the proliferating cells were dysregulated and dedifferentiated podocytes and not the parietal cells. However, this theory no longer holds, because the proliferating cells have the immunohistochemical profile of the parietal cells lining the Bowman capsule and not the podocytes.[29] In addition, podocytes normally have a low turnover rate thereby making

them an unlikely candidate for hyperplasia. Over expression of the vascular endothelial growth factor has been demonstrated in mice with collapsing glomerular lesions suggesting its possible role.[30] This dysregulation is most likely due to altered interaction between the vascular endothelial growth factor, the epithelial, and endothelial cells.[6] Injury to the renal tubules leads to microcystic dilatation of the tubules. Ultimately, all the structural and functional changes culminate in tubular atrophy and interstitial fibrosis. Although idiopathic CG is classified as a variant of FSGS, some authors recommend that it be categorized as a separate podocytopathic entity.[31]

Prognosis of CG is poor and is associated with faster progression to ESKD as compared with the other variants of FSGS.[1,3] Albaqumi et al[6] reported complete remission in 9.6%, and partial remission in 15.2% of treated patients. In our study, about half of our patients responded well with either complete (26%) or partial (19%) remission. Approximately one-fourth did not respond to treatment, and roughly one-fourth developed ESKD over a median period of 23 months from the time of biopsy. Other studies have shown a range between 7 to 30 months from biopsy diagnosis to renal failure.[12,32,33] Valeri et al[33] documented that 50% of their CG patients (n=43) progressed to ESKD. D'Agati et al,[3] in there study reported that 28% of their CG patients developed ESKD by the first year of follow up, and 47% developed ESKD by the third year of follow up.[3] The relatively good outcome in our study is perhaps due to timely diagnosis and the prompt use of strong immunosuppressive drugs. The age at presentation, serum creatinine, degree of proteinuria, and the number of glomerular collapse lesions, did not correlated with the clinical outcome or the occurrence of ESKD.

In summary, CG is a distinct pattern of glomerulopathy diagnosed by kidney biopsy, caused by various etiological factors, and commonly characterized nephrotic syndrome with rapid deterioration of renal function and resistance to immunosuppressive therapy. This article elaborates the clinico-pathological features and course of CG in Saudi patients. This study is limited by the number of patients analyzed and because the CG cases from only one center were considered. We retrospectively reviewed 12 years of renal biopsies and identified 31 patients with CG in the Saudi Arabian population at a tertiary level center. All our patients were Arabs, none of African descent, none HIV positive nor IV drug users. Most were adult males, and all presented with nephrotic syndrome. No possible etiology was identified in any of our cases. None responded to the standard steroid treatment. Progression to the ESKD was noted in approximately one fourth of our patients. Due to its relatively poor prognosis, a good understanding of this entity is important. All patients diagnosed with CG should be screened for any underlying etiology. Early recognition and immunosuppressive drugs can help improve the course of the disease. More studies are still needed to further understand the pathophysiology of this variant and to introduce preventive strategies with better treatment modalities in order to improve the prognosis of CG. APOL1 genetic testing may have potential implication for future studies. Awareness of this entity, timely renal biopsy, and diagnosis is the key to optimal management.

Acknowledgements. *The author would like to express their gratitude to the Medical Research Center at King Khalid University Hospital and the Deanship of Research at King Saud University for their support and encouragement during the preparation of this manuscript. The author would also like to thank Dr. Sayed S. Al-Esawy, Pathology Department Academic Coordinator, College of Medicine & King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia for translating the title page and abstract from English to Arabic.*

References

1. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. ***Am J Kidney Dis*** 2004; 43: 368-382.
2. Weiss MA, Daquioag E, Margolin EG, Pollak VE. Nephrotic syndrome, progressive irreversible renal failure, and glomerular "collapse": a new clinicopathologic entity? ***Am J Kidney Dis*** 1986; 7: 20-28.
3. D'Agati VD, Alster JM, Jennette JC, Thomas DB, Pullman J, Savino DA, et al. Association of histologic variants in FSGS clinical trial with presenting features and outcomes. ***Clin J Am Soc Nephrol*** 2013; 8: 399-406.
4. El-Refaey AM, Kapur G, Jain A, Hidalgo G, Imam A, Valentini RP, et al. Idiopathic collapsing focal segmental glomerulosclerosis in pediatric patients. ***Pediatr Nephrol*** 2007; 22: 396-402.
5. Gulati A, Sharma A, Hari P, Dinda AK, Bagga A. Idiopathic collapsing glomerulopathy in children. ***Clin Exp Nephrol*** 2008; 12: 348-353.
6. Albaqumi M, Soos TJ, Barisoni L, Nelson PJ. Collapsing Glomerulopathy. ***J Am Soc Nephro*** 2006; 17: 2854-2863.
7. Ross MJ, Klotman PE. HIV-associated nephropathy. ***AIDS*** 2004; 18: 1089-1099.
8. Detwiler RK, Falk RJ, Hogan SL, Jennette JC. Collapsing glomerulopathy: a clinically and pathologically distinct variant of focal segmental glomerulosclerosis. ***Kidney Int*** 1994; 45: 1416-1424.

9. Laurinavicius A, Hurwitz S, Rennke HG. Collapsing glomerulopathy in HIV and non-HIV patients: A clinicopathological and follow-up study. ***Kidney Int*** 1999; 56: 2203-2213.
10. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: A comparison of renal biopsy findings from 1976-1979 and 1995-1997. ***Am J Kidney Dis*** 1997; 30: 621-631.
11. Schwimmer JA, Markowitz GS, Valeri A, Appel GB. Collapsing glomerulopathy. ***Semin Nephrol*** 2003; 23: 209-218.
12. El-Refaey AM, Bakr A, Hammad A, Elmougy A, El-Houseeny F, Abdelrahman A, et al. Primary focal segmental glomerulosclerosis in Egyptian children: a 10-year single-centre experience. ***Pediatr Nephrol*** 2010; 25: 1369-1373.
13. Tomlinson L, Boriskin Y, McPhee I, Holwill S, Rice P. Acute cytomegalovirus infection complicated by collapsing glomerulopathy. ***Nephrol Dial Transplant*** 2003; 18: 187-189.
14. Moudgil A, Nast CC, Bagga A, Wei L, Nurmamet A, Cohen AH, et al. Association of parvovirus B19 infection with idiopathic collapsing glomerulopathy. ***Kidney Int*** 2001; 59: 2126-2133.
15. Marques LP, Pacheco GG, Rioja LS, Nunes SN, Velone ST, Santos OR. Can systemic lupus erythematosus be the cause of collapsing glomerulopathy? ***Lupus*** 2005; 14: 853-855.
16. Salvatore SP, Barisoni LM, Herzenberg AM, Chander PN, Nickeleit V, Seshan SV. Collapsing glomerulopathy in 19 patients with systemic lupus erythematosus or lupus-like disease. ***Clin J Am Soc Nephrol*** 2012; 7: 914-925.
17. Thaunat O, Delahousse M, Fakhouri F, Martinez F, Stephan JL, Noël LH, et al. Nephrotic syndrome associated with hemophagocytic syndrome. ***Kidney Int*** 2006; 69: 1892-1898.
18. Bhowmik D, Dinda AK, Gupta S, Agarwal SK, Tiwari SC, Dash SC. Multiple myeloma presenting as collapsing glomerulopathy. ***Indian J Pathol Microbiol*** 2003; 46: 233-234.
19. Markowitz GS, Appel GB, Fine PL, Fenves AZ, Loon NR, Jagannath S, et al. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. ***J Am Soc Nephrol*** 2001; 12: 1164-1172.
20. Jia N, Cormack FC, Xie B, Shiue Z, Najafian B, Gralow JR. Collapsing focal segmental glomerulosclerosis following long-term treatment with oral ibandronate: case report and review of literature. ***BMC Cancer*** 2015; 15: 535.
21. Meehan SM, Pascual M, Williams WW, Tolkoff-Rubin N, Delmonico FL, Cosimi AB, et al. De novo collapsing glomerulopathy in renal allografts. ***Transplantation*** 1998; 65: 1192-1197.
22. Gupta R, Sharma A, Agarwal SK, Dinda AK. Collapsing glomerulopathy in renal allograft biopsies: a study of nine cases. ***Indian J Nephrol*** 2011; 21: 10-13.
23. Liakopoulos V, Huerta A, Cohen S, Pollak MR, Sirota RA, Superdock K, et al. Familial collapsing focal segmental glomerulosclerosis. ***Clin Nephrol*** 2011; 75: 362-368.
24. Pollak MR, Genovese G, Friedman DJ. APOL1 and kidney disease. ***Curr Opin Nephrol Hypertens*** 2012; 21: 179-182.
25. Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, et al. APOL1 Genetic Variants in Focal Segmental Glomerulosclerosis and HIV-Associated Nephropathy. ***J Am Soc Nephrol*** 2011; 22: 2129-2137.
26. Nichols B, Jog P, Lee JH, Blackler D, Wilmot M, D'Agati V, et al. Innate immunity pathways regulate the nephropathy gene Apolipoprotein L1. ***Kidney Int*** 2015; 87: 332-342.
27. Barisoni L, Diomedi-Camassei F, Santorelli FM, Caridi G, Thomas DB, Emma F, et al Collapsing glomerulopathy associated with inherited mitochondrial injury. ***Kidney Int*** 2008; 74: 237-243.
28. Hakroush S, Cebulla A, Schaldecker T, Behr D, Mundel P, Weins A. Extensive Podocyte Loss Triggers a Rapid Parietal Epithelial Cell Response. ***J Am Soc Nephrol*** 2014; 25: 927-938.
29. Sakamoto K, Ueno T, Kobayashi N, Hara S, Takashima Y, Pastan I, et al. The direction and role of phenotypic transition between podocytes and parietal epithelial cells in focal segmental glomerulosclerosis. ***Am J Physiol Renal Physiol*** 2014; 306: 98-104.
30. Eremina V, Sood M, Haigh J, Nagy A, Lajoie G, Ferrara N, et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. ***J Clin Invest*** 2003; 111: 707-716.
31. Barisoni L, Schnaper HW, Kopp JB. A proposed taxonomy for the podocytopathies: a reassessment of the primary nephrotic diseases. ***Clin J Am Soc Nephrol*** 2007; 2: 529-542.
32. Singh HK, Baldree LA, McKenney DW, Hogan SL, Jennette JC. Idiopathic collapsing glomerulopathy in children. ***Pediatr Nephrol*** 2000; 14: 132-137.
33. Valeri A, Barisoni L, Appel GB, Seigle R, D'Agati V. Idiopathic collapsing focal segmental glomerulosclerosis: a clinicopathologic study. ***Kidney Int*** 1996; 50: 1734-1746.