Int J Clin Exp Pathol 2016;9(8):8716-8723
www.ijcep.com /ISSN:1936-2625/IJCEP0023204

Case Report

Fibrillary glomerulonephritis with anti-glomerular basement membrane antibody: a combined glomerular insult

Suhail Al-Salam[1], Mohamed Elsharif[2], Ayman Al Madani[3], Imran Zahid[4], Balsam Ahmed[5]

[1]Department of Pathology, College of Medicine and Health Sciences, UAE University, ALAIN PO Box 17666, UAE; [2]Nephrology Division, Specialist Physician, Mafraq Hospital, Abu Dhabi, UAE; [3]Chief of Nephrology Division, Consultant Nephrologist, Mafraq hospital, Abu Dhabi, UAE; [4]Nephrology Division, Consultant Nephrologist, Mafraq Hospital, Abu Dhabi, UAE; [5]Nephrology Division, Specialist Physician, Mafraq Hospital, Abu Dhabi, UAE

Received January 4, 2016; Accepted March 18, 2016; Epub August 1, 2016; Published August 15, 2016

Abstract: Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome characterized by quick and propagative deterioration of renal function with loosing 50% or more of renal function within three months. RGPN is associated with cellular crescents in more than 50% of glomeruli; hence it is called crescentic glomerulonephritis. We report a 47-year-old patient who presents with RPGN associated with fibrillary glomerulonephritis (FGN) and positive antiglomerular basement membrane (anti-GBM) antibody. In conclusion, FGN should be suspected in any case of RPGN presents with a nephrotic range of proteinuria. Although light microscopic and immunofluorescent studies in a renal biopsy are essential, electron microscopic study is the gold standard in establishing the diagnosis of FGN. FGN and Anti-GBM disease can co-exist as causes of RPGN.

Keywords: Crescentic glomerulonephritis, nephrotic syndrome, fibrillary glomerulonephritis, anti-glomerular basement membrane disease

Introduction

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome characterized by quick and propagative deterioration of renal function with loosing 50% or more of renal function within three months. RPGN is associated with cellular crescents in more than 50% of glomeruli; hence it is called Crescentic glomerulonephritis (CGN) [1]. CGN is subclassified morphologically into three subgroups; pauci-immune, anti-glomerular basement membrane (anti-GBM) antibody-associated and immune-complex associated [1]. Most of patients with paucity- immune CGN have positive serum level of antineutrophil cytoplasmic antibody (ANCA) [1]. While patients with anti-GBM antibody-associated CGN have positive serum level of anti-GBM antibody and linear membranous immunoreactivity to IgG and C3 on immunofluorescent study [1]. On the other hand, patients with immune complex-associated CGN show characteristic immunofluorescent and electron microscopic patterns of immune complex deposition within affected glomeruli. Fibrillary glomerulonephritis (FGN) is a glomerular disease characterized by the deposition of irregularly oriented, elongated, nonbranching fibrils of 10-30 nm thickness in the mesangium and along the capillary walls [2]. Clinically, patients with FGN present with nephrotic-range proteinuria, microscopic hematuria, hypertension, and progressive renal insufficiency, which are similar to our case. These findings occur in the setting of negative serological investigations, ruling out such entities as systemic lupus erythematosus, light-chain disease, and cryoglobulinemia [3]. CGN is seen in almost 5% of FGN [1, 4-7]. In this study we report CGN in a 47-yeay-old patient with FGN and positive serum anti-GBM antibody.

Case report

A 47-year-old patient, who is known to be hypertensive for 3 years, presented to the Emergency

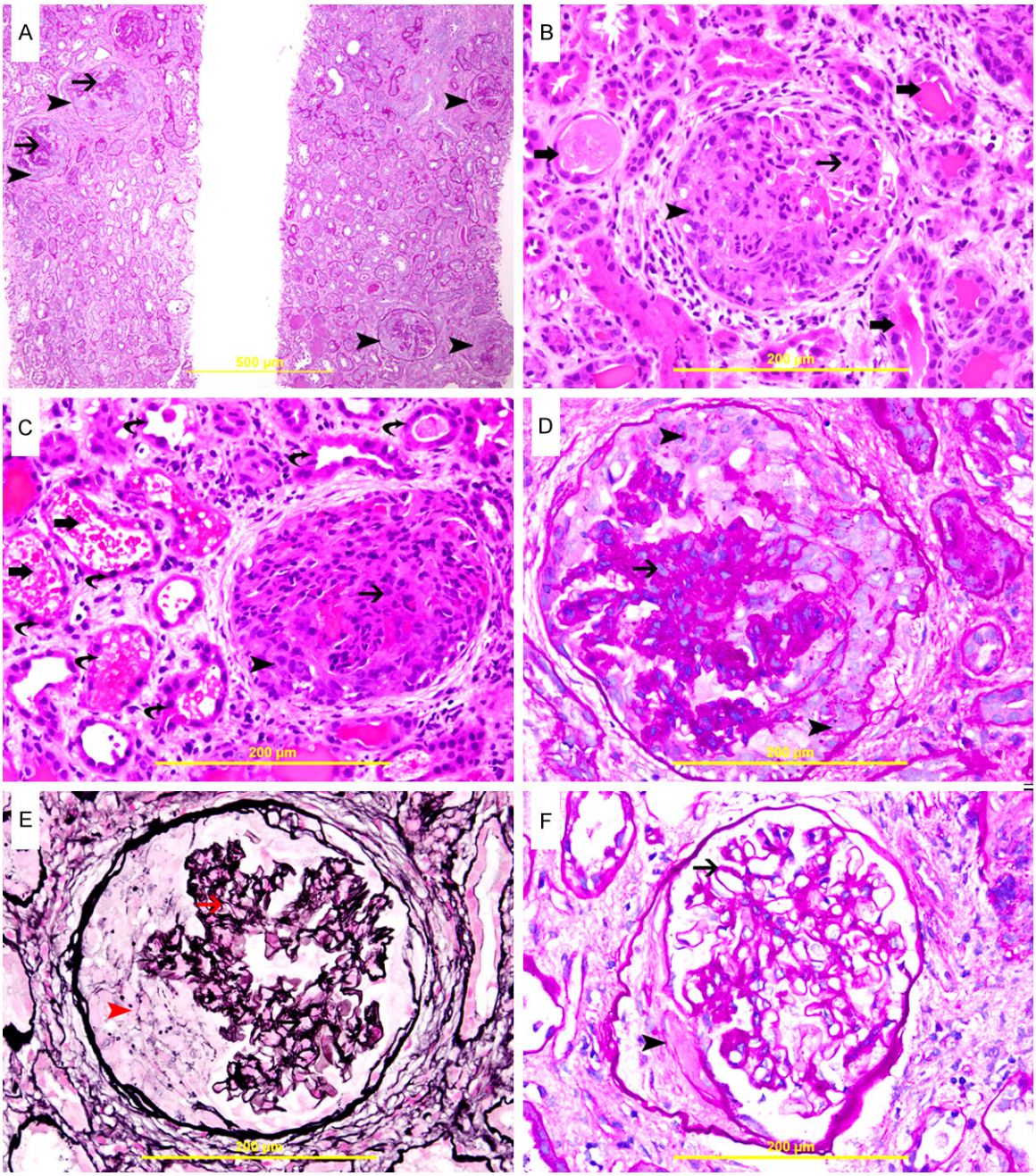

Figure 1. A. A low power view showing multiple glomeruli crescents (arrow head) surrounding collapsed glomeruli (thin arrow), periodic acid Schiff stain. B. A high power view showing a cellular crescent (arrow head) surrounding a collapsed glomerulus (thin arrow). There is also acute tubular necrosis affecting proximal convoluted tubules (thick arrow), H&E stain. C. A high power view showing a cellular crescent (arrow head) surrounding a collapsed glomerulus (thin arrow). There is also acute tubular necrosis affecting many tubules (curved arrow), some tubules have a large number of red blood cells filling the lumen (thick arrow), H&E stain. D. A high power view showing a cellular crescent (arrow head) surrounding a collapsed glomerulus (thin arrow), periodic acid Schiff stain. E. A high power view showing a cellular crescent (arrow head) surrounding a collapsed glomerulus (thin arrow), methanamine silver stain. F. A high power view showing a glomerulus with thickening of glomerular basement membrane (thin arrow) and a small fibrous crescent (arrow head).

Room (ER) with nausea, vomiting and bilateral leg edema coupled with a rapid decline in his renal function and the presence of nephrotic range proteinuria. The patient started to experi-

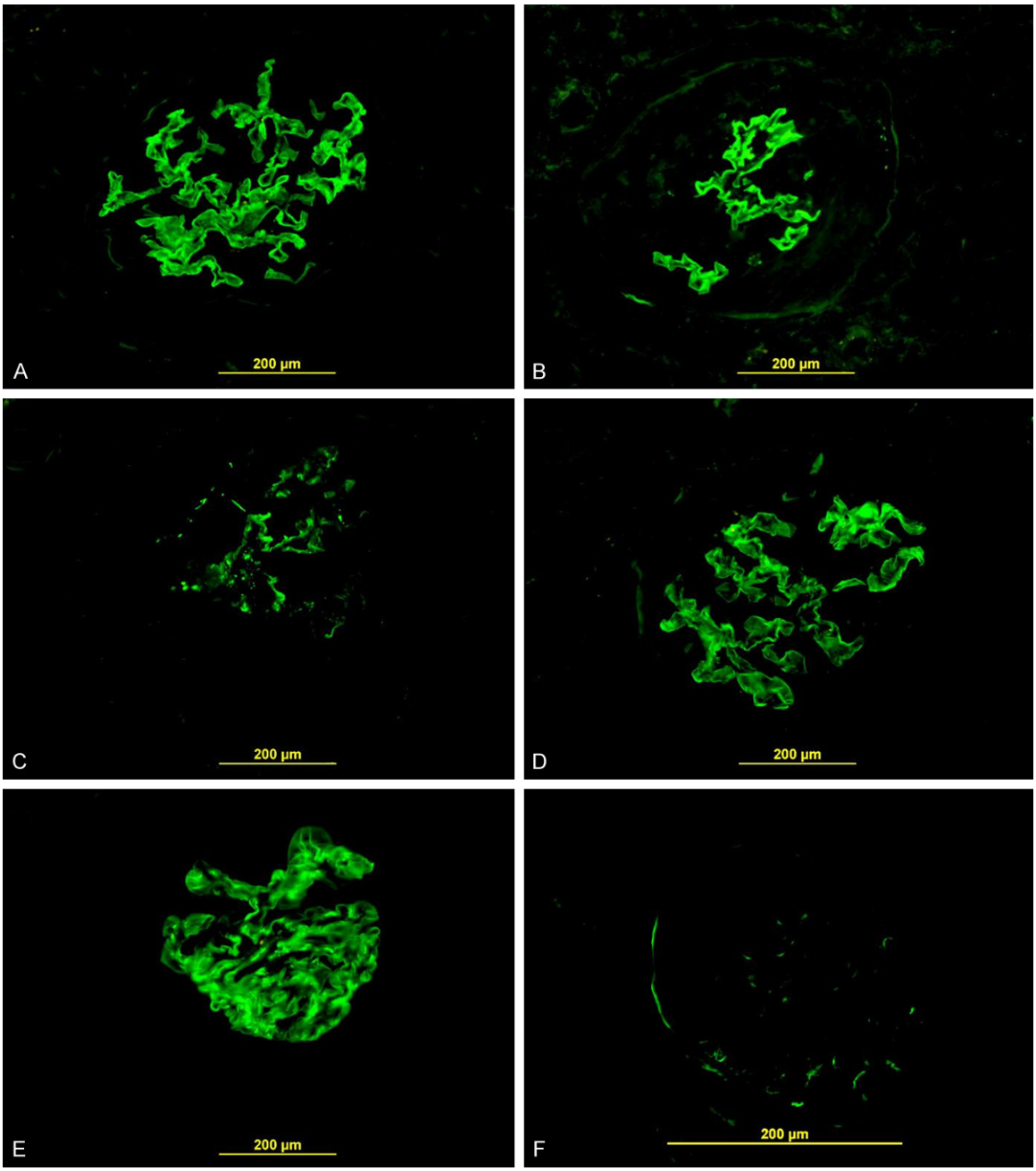

Figure 2. A, B. High power views show linear membranous immunoreactivity to IgG, C. A high power view shows linear membranous immunoreactivity to C3. D. A high power view shows linear membranous immunoreactivity to Kappa light chain. E. A high power views shows linear membranous immunoreactivity to lambda light chain. F. A high power view shows no immunoreactivity to albumin.

ence generalized body weakness, poor oral intake, nausea, vomiting and hematuria in the past 3 weeks prior to his ER visit. He denied any decrease in urine output, shortness of breath, hemoptysis, and orchest pain. He did not have similar symptoms before. His hypertension was well controlled by medication before this presentation.

On admission, his blood pressure was 165/95 mmHg, pulse rate was 60/min, respiratory rate was 18/minute, temperature was 36.5 C, and oxygen saturation was 100%. Lungs were clear to auscultation. The heart was unremarkable. There was moderate bilateral lower limb pitting edema (+2). Laboratory results showed urea 25.7 mmol/L (2.5-8), creatinine 943 micro-

mole/L (<133), total protein 42 g/L (64-83), albumin 19 g/L(35-52), Glomerular filtration rate 5 ml/minute/1.73 m^2 (>90), random blood sugar 5.8 mmol/L (2.8-8.8). Liver function tests were unremarkable. Serologic tests for antinuclear antibodies, anti-double stranded DNA antibodies, anti-neutrophil cytoplasmic antibodies, hepatitis B virus and hepatitis C virus were unremarkable. Compliment 3 and 4 levels were within normal range. Anti-glomerular basement membrane antibody was positive.

The patient had a nephrotic range of proteinuria with numerous red blood cells in the urine.

The complete blood count was remarkable for Hemoglobin of 75 gm/L (131-172), RBC 2.8×10^{12}/L (4.2-5.6), MCV 78.6 fL (81-101), MCH 26.8 pg (27-35), RDW 17.7% (11.6-14.8), platelets count 108×10^9/L (140-400), mean platelets volume 12.2 fL (7.3-9.7), WBC 7.8×10^9/L, lymphocytes 0.16×10^9/L (1-3.5), neutrophils 7.6×10^9/L (2-8).

The renal function deteriorates rapidly which necessitates starting hemodialysis and arranging for kidney biopsy.

Pathologic findings

Renal biopsy was performed and we received 3 cores of 1.5 cm in length and 0.1 cm in diameter each. Light microscopic examination reveals renal tissue consists of cortex, medulla and contains 50 glomeruli; 3 of which are globally sclerosed. There are 45 cellular crescents, which compress the affected glomeruli (**Figure 1**). 5 glomeruli are free of crescents and show thickening of glomerular basement membrane with meningeal expansion (**Figure 1F**). Foci of acute tubular injury are seen (**Figure 1B**, **1C**). Foci of mild tubular atrophy are also noticed. Some of the tubules show intratubular casts. In addition, some tubules show intratubular free red blood cells (RBC) filling the lumen (**Figure 1C**) and sometimes forming RBC casts. There are foci of mild mixed interstitial inflammatory cells infiltration consists mainly of lymphocytes. Periglomerular fibrosis is seen in 6 glomeruli. Few foci of mild interstitial fibrosis are appreciated. Sampled blood vessels are unremarkable. Immunofluorescent examination reveals linear membranous staining for IgG (+2), C3 (+2), Kappa light chain (+2) and Lambda light chain (+2) (**Figure 2**). Electron microscopic study reveals thickening of glomerular basement membrane 0.55 μm±0.15 (0.23-0.48) with a range of (0.41-0.96 μm) as well as deposition of fibrillary material in the basement membrane and mesangium (**Figure 3**). The intramembranous, randomly oriented fibrils have a mean diameter of 13.6 nm±2.13 and a range of (10-18) that infiltrate and thicken the glomerular basement membrane. The fibrils lack hollow centers and parallel stacking. Mesangial deposition of these fibrils is also seen (**Figure 3**). There is severe effacement of foot processes of a podocytes. Congo red stain for amyloid material was negative.

Discussion

Crescentic glomerulonephritis is a serious disorder that must be diagnosed quickly and accurately so that appropriate management can be initiated as quickly as possible, since delay in diagnosis and treatment will have a major negative impact on the outcome due to the rapidly progressing loss of renal function. Clinicians should have a high index of suspicion especially, on facing patients with rapid deterioration of renal function, and quickly referring them to nephrologists. The diagnosis of CGN depends entirely on the identification of cellular crescents in 50% or more of sampled glomeruli.

Interestingly, the starting event in crescent formation is injury to the glomerular capillary endothelium and GBM. The damaged glomerular endothelium and GBM will permit passage of fibrin and other plasma proteins to Bowmann's space, which stimulate the proliferation of visceral and parietal epithelium, as well as recruitment of inflammatory cells especially T lymphocytes and macrophages [8]. This cellular process is accompanied by a release of inflammatory cytokines and activation of coagulation cascade [8]. In this study we show a severe CGN with more than 90% of glomeruli showing cellular crescents that compress affected glomeruli leading to severe deterioration of GFR and renal function. We also show a linear glomerular membranous immunofluorescent staining with IgG and C3 as well as positive serum level for anti-GBM antibody; findings support the diagnosis of anti-GBM-associated CGN.

Anti-GBM antibodies bind primarily to the aminoterminal region of the NC1 domain of the α3

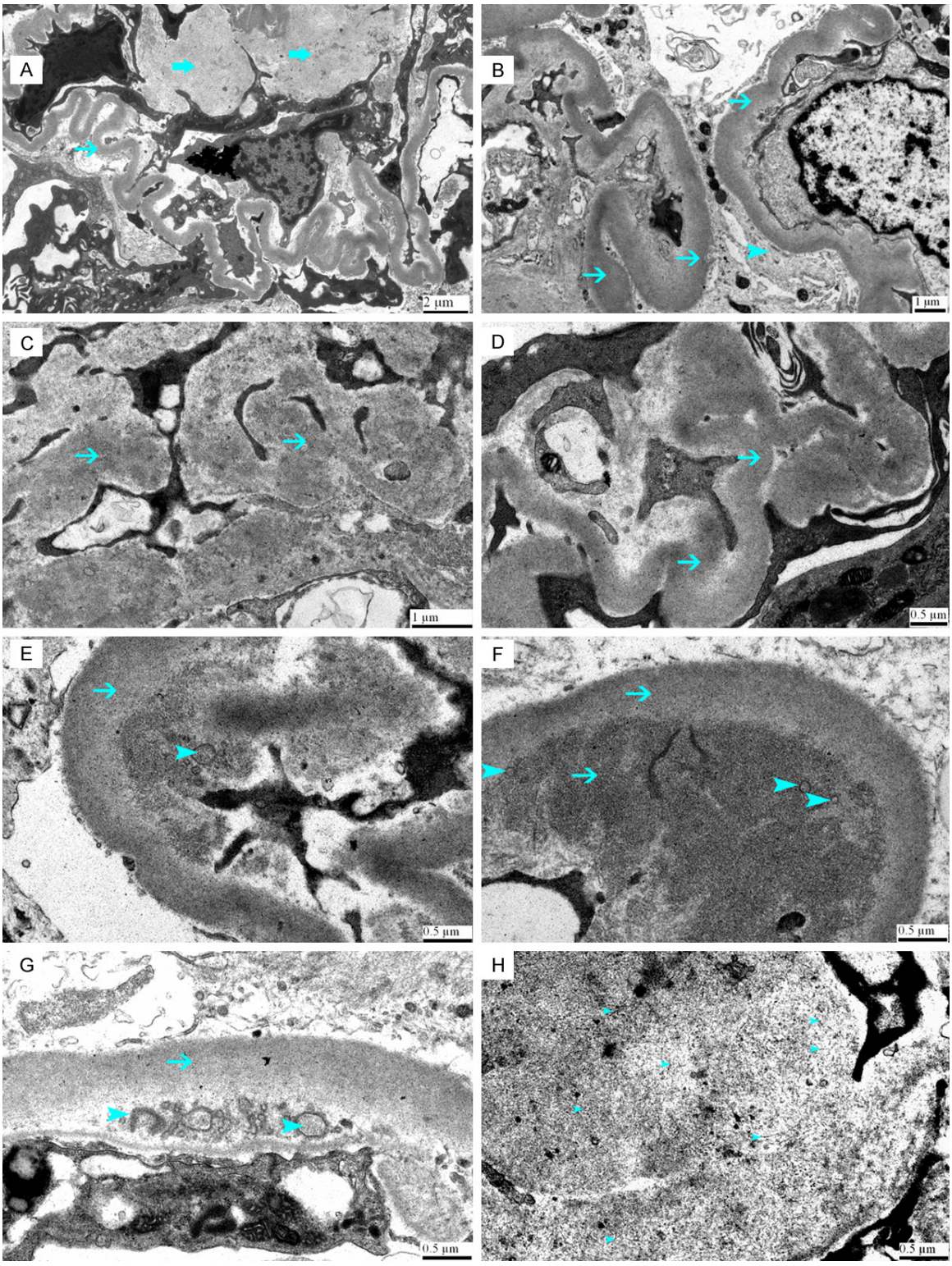

Figure 3. A. Electron micrograph of a glomerulus showing thickening of glomerular basement membrane with deposition of fibrillary material (thin arrow) in the basement membrane and mesangium (thick arrow). B. Electron micrograph of a glomerulus showing thickening of glomerular basement membrane with deposition of fibrillary material (thin arrow) in the basement membrane. There is effacement of foot processes of a podocyte (arrow head). C. Electron micrograph of a glomerulus showing deposition of fibrillary material (thin arrow) in the mesangium. D. Electron micrograph of a glomerulus showing thickening of glomerular basement membrane with deposition of fibrillary material (thin arrow) in the basement membrane. E-G. Intramembranous, randomly oriented fibrils of mean

13.6 nm diameter (thin arrow) that infiltrate and thicken the glomerular basement membrane. The fibrils lack hollow centers and parallel stacking. There is subendothelial accumulation of fibrils arranged in parallel stacks (arrow head). H. Randomly oriented fibrils of mean diameter of 13.6 nm (arrow head).

chain of type IV collagen and this binding is associated with the development of progressive renal disease [9].

Mutations in the COL4A3 gene which codes the α3 chain of collagen IV NC1 [10] have not been found in any experimental or clinical studies, which suggests no role of this gene in the pathogenesis of the disease. There are two distinct epitopes; EA and EB, for the anti-GBM-Ab [11]. Reports have suggested that EA and EB are hidden epitopes for B lymphocytes, covered by the quaternary structure of the hexamers created by bridges among monomers adjacent to NC1 chains [12]. The disconnection of these NC1 chains exposes the pathogenic epitopes of the α3 and α5 chains, leading to production of anti-GBM antibody. The crucial decisive factor of exposure of these epitopes remains unknown. However, it is assumed to be the result of a combination of factors such as genetic susceptibility, post-transcription modifications, epitope extension and environmental factors [13].

Moreover, cell-mediated mechanisms have been incriminated in the initiation of anti-GBM antibody production. T cells play a key role in response to exposure to the cryptic EA and EB epitopes, generating signals that enable B-cell proliferation and production of anti-GBM antibody [14].

High serum level of anti-GBM antibody in our patient can damage glomerular endothelial cells and GBM leading to cellular crescents [1, 8]. The hematuria and RBC casts within renal tubules also supports anti-GBM antibody damaging effect on glomerular endothelial cells and basement membrane leading to cellular crescents formation. Our patient has clear lungs and denied any history of hemoptysis, which excludes Goodpasture syndrome and supports restricted renal anti-GBM disease.

Since the establishment of laboratory tests to detect anti-GBM antibodies the number of diagnostic biopsies have been enormously decreased. Now, biopsies are more significant for determining a prognosis, computing epithelial and fibrotic crescents to decide whether to continue with immunosuppression therapy or to prescribe more conservative treatment [15].

We also show thickening of GBM with intramembranous deposition of randomly oriented, Congo-red negative fibrils of 10-18 nm in diameter that infiltrate and thicken the glomerular basement membrane; features confirm the diagnosis of FGN.

However; the unusual and important features of this case of FGN are the presence of global linear IgG staining, largely limited to capillary walls with active cellular crescents in more than 90% of the glomeruli and positive anti-GBM antibody. Cellular crescents can be seen in FGN but this degree of severity of the disease with more than 90% cellular crescents is rarely reported in FGN-associated CGN [1].

Although it has been suggested that FGN is immune mediated [16], the exact mechanism of the disease remains unclear. Whereas fibril deposition is almost always limited to the kidney, there have been observations suggesting that FGN is a systemic, rather than a renal-limited disease as it has been shown that FGN can recur in renal transplant recipients [3], suggesting a systemic factor in the recipient.

An important question can be raised here; which event starts first; Anti-GBM antibody or FGN? The past history of the patient did not show any feature of acute renal insufficiency, which usually seen in anti-GBM antibody, besides the patient denied any previous presentation with features similar to the current illness. This might exclude anti-GBM disease as being the primary initiator and support its recent development with the initiation of current illness. Besides, it is very rare to have nephrotic range of proteinuria in CGN due to anti-GBN disease [17], hence the presence of heavy proteinuria in our case might be mainly due to FGN.

Guerin et al suggests the possibility of repeated insults to the GBM [18], may cause alterations to its structure, possibly through local inflammation, with infiltrating leukocytes-releasing granular enzymes and free radicals. This

could favor the exposure of the globular domain NC1 of α3 chain of collagen IV, which contains the cryptic EA and EB epitopes, triggering an autoimmune response. This can be triggered with different kinds of insults including extracorporeal short wave therapy [18], ureteric obstruction [19], and monoclonal gammopathy [20].

We propose glomerular basement membrane insult might have been occurred due to deposition of fibrils that might uncover cryptic epitopes and initiates anti-GBM antibody. However, these are just speculations and necessitate further studies.

We think that the high percentage of cellular crescents in our case is due to the combined insults to glomerular endothelium and GBM by deposited fibrils and anti-GBM antibody.

Our literature search identified a patient with FGN who was diagnosed as having anti-GBM-glomerulonephritis based on immunofluorescence microscopy findings [21] and another case of FGN which was diagnosed of having anti-GBM antibody by immunoassay test [22].

In conclusion, FGN should be suspected in any case of RPGN presents with a nephrotic range of proteinuria. Although light microscopic and immunofluorescent studies in a renal biopsy are essential, electron microscopic study is the gold standard in establishing the diagnosis of FGN. FGN and Anti-GBM disease can co-exist as causes of RPGN.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Suhail Al-Salam, Department of Pathology, College of Medicine and Health Sciences, UAE University, ALAIN PO Box 17666, UAE. Tel: +97137137464; Fax: +9713767-1966; E-mail: suhaila@uaeu.ac.ae

References

[1] Jennette JC. Rapidly progressive crescentic glomerulonephritis. Kidney Int 2003; 63: 1164-77.

[2] Nasr SH, Valeri AM, Cornell LD, Fidler ME, Sethi S, Leung N, Fervenza FC. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. Clin J A Soc Nephrol 2011; 6: 775-784.

[3] Pronovost PH, Brady HR, Gunning ME, Espinoza O, Rennke HG. Clinical features, predictors of disease progression and results of renal transplantation in fibrillary/immunotactoid glomerulopathy. Nephrol Dial Transplant 1996; 11: 837-842.

[4] Sharma P, Kuperman M, Racusen L, Geetha D. Fibrillary glomerulonephritis presenting as rapidly progressive glomerulonephritis. Am J Kidney Dis 2012; 60: 157-9.

[5] Mahajan S, Kalra V, Dinda AK, Tiwari SC, Agarwal SK, Bhowmik D, Dash SC. Fibrillary glomerulonephritis presenting as rapidly progressive renal failure in a young female: a case report. Int Urol Nephrol 2005; 37: 561-4.

[6] Soma J, Sato K, Nakaya I, Yahata M, Sakuma T, Sato H. Systemic non-amyloidotic fibril deposition disease: a probable variant form of fibrillary glomerulonephritis. Clin Nephrol 2011; 75: 74-9.

[7] Ovuworie C, Volmar K, Charney D, Kravet S, Racusen L. Rapidly progressive renal failure with nephrotic syndrome in a patient with type 2 diabetes mellitus: the differential of fibrillary deposits. Am J Kidney Dis 2000; 35: 173-7.

[8] Thorner PS, Ho M, Eremina V, Sado Y, Quaggin S. Podocytes contribute to the formation of glomerular crescents. J Am Soc Nephrol 2008; 19: 495-502.

[9] Kambham N. Crescentic Glomerulonephritis: an update on pauci-immune and anti-GBM diseases. Adv Anat Pathol 2012; 19: 111-24.

[10] Persson U, Hertz JM, Carlsson M, Hellmark T, Juncker I, Wieslander J, Segelmark M. Patients with Goodpasture's disease have two normal COL4A3 alleles encoding the NC1 domain of the type IV collagen alpha 3 chain. Nephrol Dial Transplant 2004; 19: 2030-5.

[11] Borza DB, Netzer KO, Leinonen A, Todd P, Cervera J, Saus J, Hudson BG. The Goodpasture autoantigen: Identification of multiple cryptic epitopes on the NC1 domain of the alpha3(IV) collagen chain. J Biol Chem 2000; 275: 6030-7.

[12] Vanacore RM, Friedman DB, Ham AJ, Sundaramoorthy M, Hudson BG. Identification of S-hydroxylysyl-methionine as the covalent cross-link of thenoncollagenous (NC1) hexamer of the alpha1alpha1alpha2 collagen IV network: a role for the post-translational modification of lysine 211 to hydroxylysine 211in hexamer assembly. J Biol Chem 2005; 280: 29300-10.

[13] Zhou XJ, Lv JC, Zhao MH, Zhang H. Advances in the genetics of antiglomerular basement membrane disease. Am J Nephrol 2010; 32: 482-90.

[14] Kluth D and Rees A. Anti-glomerular basement membrane disease. J Am Soc Nephrol 1999; 10: 2446-2453.
[15] Kambham N. Crescentic Glomerulonephritis: an update on pauci-immune and anti-GBM diseases. Adv Anat Pathol 2012; 19: 111-24. (Lee RW, D'Cruz DP. Pulmonary renal vasculitis syndromes. Autoimmun Rev 2010; 9: 657-60.
[16] Rostagno A, Vidal R, Kumar A, Chuba J, Niederman G, Gold L, Frangione B, Ghiso J, Gallo G. Fibrillary glomerulonephritis related to serum fibrillar immunoglobulinfibrinectin complexes. Am J Kidney Dis 1996; 28: 674-684.
[17] Quiroga B, Vega A, Rivera F, López-Gómez JM; Spanish Registry of Glomerulonephritis. Crescentic glomerulonephritis: data from the Spanish Glomerulonephritis Registry. Intern Med J 2015; 45: 557-62.
[18] Guerin V, Rabian C, Noel LH, Droz D, Baron C, Lallemand F, Jungers P. Anti-glomerular-basement-membrane disease after lithotripsy. Lancet 1990; 335: 856-7.
[19] Takeuchi Y, Takeuchi E, Kamata K. A possible clue for the production of anti-glomerularbasementmembrane antibody associated with ureteral obstruction and hydronephrosis. Case Rep Nephrol Dial 2015; 5: 87-95.
[20] Maes B, Vanwalleghem J, Kuypers D, Van Damme B, Waer M, Vanrenterghem Y. IgA antiglomerular basement membrane disease associated with bronchial carcinoma and monoclonal gammopathy. Am J Kidney Dis 1999; 33: E3.
[21] Nilajgi S, Killen JP, Baer R, Renaut P, Mantha M. Fibrillary glomerulonephritis. NDT Plus 2011; 4: 413-415.
[22] Momose A, Nakajima T, Chiba S, Kumakawa K, Shiraiwa Y, Sasaki N, Watanabe K, Kitano E, Hatanaka M, Kitamura H. A case of fibrillary glomerulonephritis associated with thrombotic microangiopathy and anti-glomerular basement membrane antibody. Nephron Extra 2015; 5: 30-8.