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Case Report

Coexistence of Focal Segmental Glomerulosclerosis and Immunoglobulin-A Nephropathy: What a Diagnostic Challenge

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Abstract

Focal Segmental Glomerulosclerosis (FSGS) is the commonest cause of nephroticsyndrome in adults. Immunoglobulin-A Nephropathy (IgAN) is a common cause of hematuria, however it is uncommon to present with 1ephritic syndrome. Recent studies showed that nephroticsyndrome in IgAN could be secondary to podocyte injury with segmental sclerosis similar to the FSGS. Here, we are reporting a case of coexisting FSGS and IgAN as two different renal pathologies.

Keywords: Focal Segmental Glomerulosclerosis, Immunoglobulin-A Nephropathy, Nephrotic syndrome.

INTRODUCTION

FSGS is a disease of progressive scarring involving portions of some glomeruli with foot processes effacement (deMik et al., 2013; D'Agati, 2003; D'Agati et al., 2004; Korbet, 2012). It causes up to 35% of the idiopathic 1ephritic syndrome in adults worldwide (deMik et al., 2013; Korbet, 2012) and 21.3-27.6% of primary glomerulonephritis in Saudi Arabia (Huraib et al., 2000; Nawaz et al., 2013). The sclerotic lesions in FSGS develop secondary to either inflammation/necrosis or podocyte injury due to hemodynamic changes from nephron loss (Cook, 2011).

IgAN is a glomerular disease secondary to IgA deposits in the mesangium and glomerular capillaries. Clinical spectrum ranges between asymptomatic microscopic hematuria with/out proteinuria and full spectrum nephritic-nephrotic syndrome. It is uncommon to present with pure 1ephritic syndrome except in children and young adolescent. The incidence of IgAN accounts between 6.4% and 11.5% of renal biopsies in some centers in Saudi Arabia (Nawaz et al., 2013).

It was thought that segmental sclerosis in Oxford classification happens secondary to inflammation (Roberts et al., 2009). However, a study by Hill et al. suggested that podocytopathy injury in IgAN can occur similarly to primary FSGS (Hill et al., 2011). He and his group found out that "the majority of cases of IgAN can be interpreted as representing one or another variant of FSGS. Hence, interpreting IgAN in terms of FSGS emphasizes the role that podocyte lesions may play in the pathogenesis and progression of the disease" (El Karoui et al., 2011). We are reporting a case of IgAN coexisting with FSGS as dual pathologies that showed

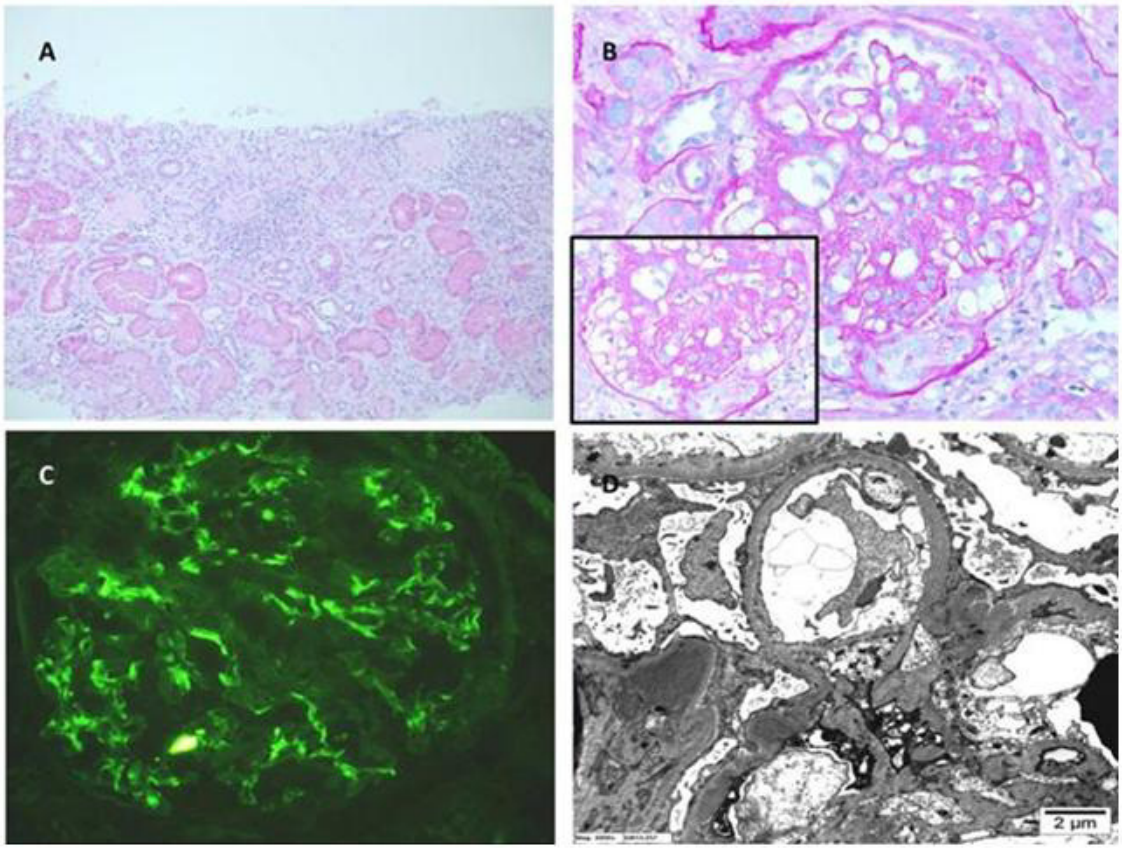

Figure 1. Renal Biopsy

A. Light microscopy shows interstitial fibrosis, tubular atrophy, glomerular sclerosis and patchy inflammation. (Hematoxylin and Eosin stain, original magnification x200).
B. Light microscopy of a glomerulus shows asubtotal collapse of the glomerular tuft with overlying epithelial hyperplasia. Inset: Intracytoplasmic PAS positive droplets are noted in the podocytic cytoplasm. (Periodic-Acid-Schiff stain, original magnification x600).
C. Immunofluorescence microscopy shows global mesangial staining for IgA. (Anti-IgA antibody immunofluorescence, original magnification x400).
D. Electron microscopy shows both the diffuse epithelial cell injury including effacement of the epithelial cell processes with microvillous degeneration of the epithelial cell cytoplasm and the mesangial as well as the paramesangialdense deposits. (Uranyl acetate, lead citrate stain, original magnification x8000).

similar changes as discussed by Hill and his coworkers.

Case presentation

Mr. A. is a 20-year-old Saudi male who was referred to nephrology clinic with newly diagnosed hypertension (150/77 mmHg) and pitting edema of legs. Systemic review and family history of renal disease were negative. His BMI was 43 kg/m^2. Renal ultrasound showed normal sized kidneys with normal echogenicity. His investigations showed microscopic hematuria, proteinuria (7.5 g/day), low serum albumin (28 g/L), elevated serum creatinine (118 umol/L), normal total cholesterol (4.9 mmol/L), and normal complements [C3 (1.47 g/L) and C4 (0.423 g/L)]. Serological tests were negative including anti-Nuclear antibodies, Double-Stranded DNA antibodies, Hepatitis B, C and HIV. He underwent renal biopsy showing IgA Nephropathy with diffuse podocyte injury and evidence of concomitant FSGS of peri-hilar and NOS (not otherwise specified) variants (Figure 1).

He was followed-up at nephrology clinic and was treated with Irbesartan. Prednisone wasn't given due to his obesity. Two years later, his follow-up investigation showed a trace microscopic hematuria, persistent heavy proteinuria (6.28 g/day), low serum albumin (34 g/L), worsening serum creatinine (483 mmol/L) and normal total cholesterol (4.8 mmol/L). Renal biopsy was repeated showing worsening findings of IgA nephropathy with mesangialhypercellularity, glomerular segmental scar-ring and extensive tubulointerstitial scarring (Figure 2).

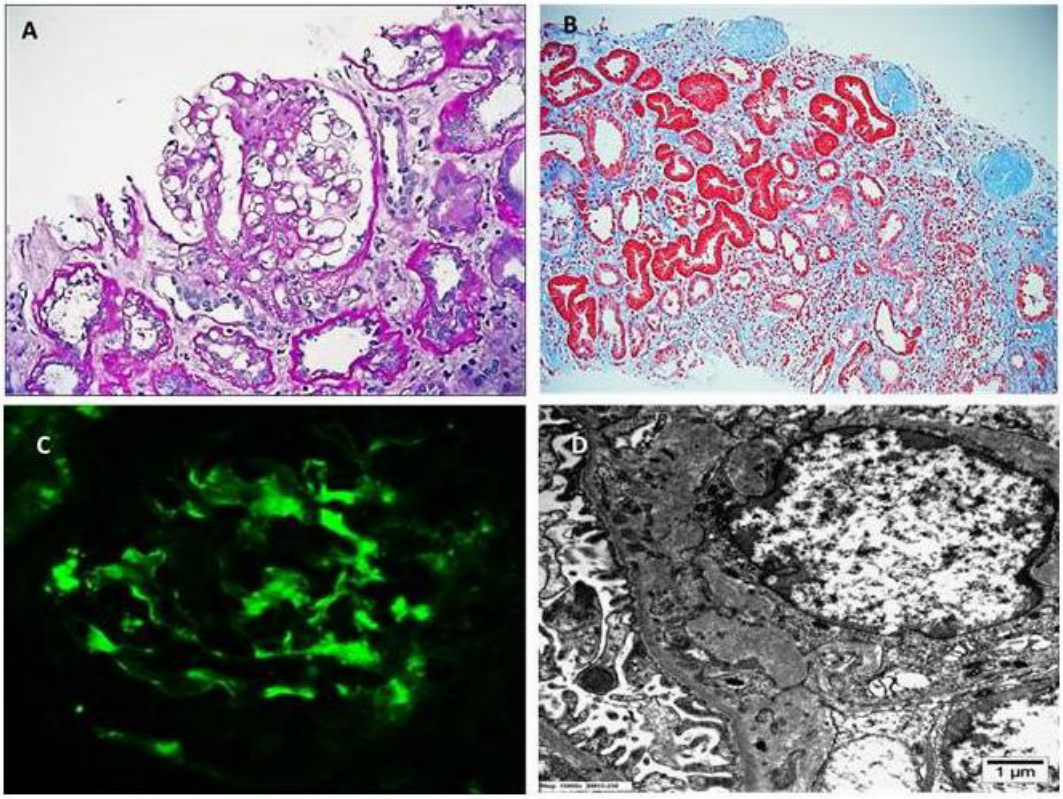

Figure 2. Repeated Renal Biopsy

A. The photomicrograph shows a glomerulus with segmental sclerosis of a glomerular tuft with focal mild mesangial matrix expansion (Periodic Acid Schiff stain; original magnification x400).
B. The photomicrograph shows renal parenchyma with global glomerular sclerosis, extensive interstitial fibrosis and tubular atrophy with associated mononuclear inflammatory infiltrate and patchy compensatory hypertrophy of the tubules (Hematoxylin and Eosin stain; original magnification x200).
C. Immunofluorescence study showing intense the diffuse mesangial positivity for IgA (Anti-IgA antibody immunofluorescence, original magnification x400).
D. The ultrastructural photomicrograph shows few small electron-dense immune deposits in the mesangium. (Uranyl acetate, lead citrate, x 15000).

DISCUSSION

The kidney biopsy of this case showed on light microscopy number of glomeruli exhibited moderate podocyte hyperplasia and hypertrophy with wrinkling and collapse of the underlying glomerular capillary loops. Some protein resorption droplets were noted in the Bowman's space and tubules. There was no endocapillary proliferation. Tubular atrophy and interstitial fibrosis involved about 20% of the sampled cortex. In addition, there was some arteriosclerosis and arteriolar hyalinosis. Immunofluorescence microscopy revealed a diffuse moderate granular IgA staining in the mesangium and focal mild to moderate mesangial positivity with C3 and lambda. The staining of IgG and C1q were negative. On electron microscopy, there was an almost diffuse effacement of the epithelial cell foot processes. Scattered electron dense immune deposits were identified in the mesangial and paramesangial areas.

Segmental sclerosis develops through one of the followingmechanisms: (1) post-inflammatory scarring secondary to endocapillary/ extracapillary proliferation or to glomerular tuft necrosis, or (2) compensatory scarring secondary to hemodynamic stress from disease-associated nephron loss along with podocytop-athicsequalae. However, segmental sclerosis in IgAN is thought to develop secondary to direct cytotoxic effect of IgA1 molecules in the glomerular mesangium (Cook, 2011). The segmental lesions in most cases of IgAN are indeterminate; however specific histopathological features can be indicative of dual pathologies. They include marked podocyte hypertrophy and proliferation, intracapillaryhyalinosis and almost diffuse effacement of the epithelial cell foot processes along with nephrotic syndrome (El Karoui et al., 2011). Our case presented with nephrotic syndrome, segmental sclerosis with epithelial cell proliferation, no necro-inflammatory lesions, and cystic dilatation of tubules with almost diffuse

effacement of the podocytes. All these findings are highly indicative of dual pathologies of IgAN with primary FSGS.

It may be argued that this is merely a case of incidental IgA deposition in a case of nephrotic syndrome with FSGS, but the presence of multiple electron dense deposits in the mesangium along with the dominant IgA staining on immunofluorescence firmly establishes them as cases of IgA nephropathy (Suzuki et al., 2003). It may also be argued that the podocyte hypertrophy/hyperplasia isactually a crescent formation, but El Karoui et al. in their study regarded such lesions as pseudo-crescents if they were found in the setting of FSGS (El Karoui et al., 2011).

CONCLUSION

We recommend examining carefully the renal biopsy of IgA nephropathy patients with segmental sclerosis for intracapillaryhyalinosis, podocyte hyperplasia and hypertrophy and diffusing epithelial cell foot processes effacement as they favor dual pathologies of IgANwith FSGS since they may create a diagnostic dilemma and affect the prognosis and management, as it was found by El Karoui et al. (2011).

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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