A Case Report

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A Rare Case Report of Collapsing Glomerulopathy Superimposed on Advanced Diabetic Nephropathy

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Abstract

Diabetic nephropathy is the leading cause of Chronic Kidney Disease(CKD) and End Stage Renal Disease(ESRD) in India and worldwide. Several forms of non-diabetic kidney disease may superimpose and alter the natural course, prognosis and management of diabetic nephropathy (DN). The causes of Collapsing glomerulopathy are idiopathic or secondary to various forms of glomerular diseases. The association between collapsing glomerulopathy and diabetic nephropathy has not been reported frequently. Here we report a rare case of a patient from Government Rajaji Medical College, Madurai, India with type 2 diabetes mellitus presented with rapidly progressive renal failure. Renal biopsy was indicative of collapsing glomeruolpathy superimposed on advanced diabetic nephropathy.

Introduction

Diabetic kidney disease is the leading cause of CKD and ESRD worldwide. The natural course of diabetic kidney disease may be affected by various non-diabetic kidney diseases. Those insults may superimpose on diabetic nephropathy and alter the course of diabetic kidney disease. Collapsing glomerulopathy represents severe form of podocyte injury. The association between diabetic nephropathy and collapsing glomerulopathy has been reported once in India.(1) Here we report a patient with uncontrolled type 2 diabetes, presented with rapidly progressive renal failure. Renal biopsy was indicative of collapsing glomerulopathy superimposed on advanced diabetic nephropathy.

Case Report

A 45 year old man with type 2 diabetes for 15 years, hypertension for 15 years and no history of renal dysfunction in the past, presented to the ER with acute pulmonary edema and renal failure. Fundus examination revealed grade II hypertensive retinopathy. His serum creatinine was 7mg/dl. His previous creatinine was not available. He was on insulin. H.Mixtard and Tab Amlodipine. Blood analysis showed total count 9900, Hb 9.4gms/dl, Urea 182mg/dl, creatinine 7mg/dl. His spot protein creatinine ratio was 8. Urine examination showed albumin 4+, no RBC, 2-4 pus cells, no casts. Peripheral study report and LDH levels were within normal levels. Serum albumin was 3.0mg/dl. Viral serology for Hepatitis B, Hepatitis C, HIV, EBV, Parvovirus and CMV were negative. Serum complements, ASO titre, ANCA titre were within normal limits. Covid IgG titer was found be negative. Serum electrophoresis was not suggestive of monoclonal gammopathy. Urine culture showed no growth. Ultrasound abdomen showed right and left kidney of dimensions 10.2*3.5mm and 10.8*3.8mm respectively with cortico-medullary differentiation partly maintained. Renal artery Doppler showed normal study.

Renal Biopsy was done. Light microscopy showed thirteen glomeruli and 10 were globally sclerotic. Collapse of the glomerular tuft with podocyte hyperplasia and hyaline globules was observed in one glomerulus. Remaining two viable glomeruli show increased mesangial matrix. No endocapillary hypercellularity, cellular crescent or fibrinoid necrosis of the glomerular capillary tuft observed. Interstitial fibrosis and tubular atrophy was around 80-90%. Artery showed medial hypertrophy. In Immunofluroscence IgG (1+) showed linear positivity over the glomerular and tubular basement membranes. Kidney biopsy showed features of collapsing glomerulopathy superimposed on advanced diabetic nephropathy. Other secondary causes of collapsing glomerulopathy were ruled out. Patient is on renal replacement therapy now.

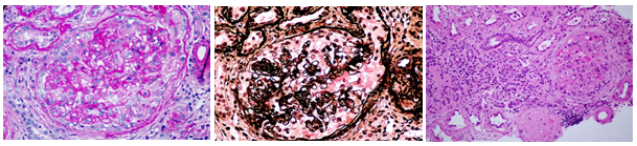

Figure 1: Collapsed glomerular tuft with hyperplasia of overlying podocytes in our patient with advanced diabetic nephropathy.

Discussion

Collapsing glomerulopathy is often seen in association with HIV infection. In this setting the kidney disease is also called HIV

associated nephropathy (HIVAN). Collapsing FSGS has also been increasingly recognized in the non HIV infected patients.(2) In a retrospective study including 620 patients with Type 2 diabetes mellitus performed in the United States, Sharma et al. reported DKD, NDKD and DKD+NDKD prevalence as 37%, 36% and 27%, respectively. In the NDKD patient group, the most frequently seen cause was FSGS (22%), followed by hypertensive nephrosclerosis (18%) and acute tubular necrosis (ATN) (17%). In the DKD+NDKD patient group, the leading cause was ATN (43%) [3].In a study by Lakshminarayna et al in India NDKD was found in 50.71% (36 of 71) of participants. Among the NDKD, 69.44% (25) had primary glomerular diseases (PGDs), 16.67% (6) had tubulointerstitial diseases (TIDs), and 13.89% (5) had secondary glomerular diseases (SGDs). IgA nephropathy (IgAN) was the most common among PGDs affecting 28% (7) of participants, followed by postinfective glomerulonephritis (PIGN) in 20% (5). Acute interstitial nephritis (AIN) was the most common among TIDs found in 50% (3) of participants, followed by chronic tubulointerstitial nephritis (CTIN) in 33.33%. Primary amyloidosis was the most common among SGDs affecting 40% (2), followed by nonamyloid deposition disease 20% (1), antineutrophil cytoplasmic antibody (ANCA) related pauci-immune glomerulonephritis in 20% (1) (4) .

Detwiler et al(5) established collapsing glomerulopathy as a distinct type of idiopathic FSGS with black racial preponderance. The incidence of CG in the native kidney biopsy was 2%. The median age of presentation was 30-40 years. Most studies have shown a male preponderance. Infections like HIV,CMV, Parvovirus, EBV, SARS-COV-2, Malaria were found to be associated with CG. Autoimmune causes of CG include Still's disease, SLE, multiple myeloma and MCTD. Drugs that cause CG include bisphosphonates, interferons, anabolic steroids, CNI and mTOR inhibitors. IgA nephropathy and advanced Diabetic glomerulopathy may superimpose on CG. Other rare causes of CG include TMA, post transplant rejection, renal infarction. (6)

As biopsies are not regularly done in diabetic kidney disease and due to the focal nature of the CG, the association of CG and diabetes has not been widely reported. (7) The pathogenesis of CG involves epithelial cell injury leading to cell cycle dysregulation and proliferation.(8) Podocytes produce VEGF which is over expressed in diabetics. High glucose levels cause the over expression of VEGF. The over expression of VEGF may play a major role in the development and progression of proteinuria and CG. Anti VEGF therapy in rodents has been shown to reduce the proteinuria in experimental models. Over expression of VEGF also led to CG in the mouse models. (9)

Diabetes affects all the compartments of kidney.(10) GBM thickening, extracellular matrix accumulation and mesangial expansion are observed in the glomeruli. Wrinkling and retraction of the capillary walls) with nodular mesangial matrix accumulation may be seen in diabetic kidney disease depending on the class of diabetic nephropathy. Various studies proposed that renal ischemia may play a role in causing glomerular collapse.

Renal disease in diabetes especially type 2 diabetes are heterogeneous. Different patterns of renal injury ranging from pure vascular sclerosis, glomerular scarring, podocyte ischemia and injury may be seen with or without typical diabetic glomerular lesions. Microvascular injury characterized by arteriosclerosis and arteriolar hyalinosis in patients with diabetic nephropathy could lead to glomerular ischemia and podocyte injury causing collapsing glomerular lesion similar to other forms of CG seen in native and transplant kidneys. (11) The glomerular collapse in diabetic kidney disease in unique. Here the mesangial matrix expansion prevents complete collapse of the glomeruli. (12). Renal biopsy of our patient showed collapse of the glomerular tuft with podocyte hyperplasia and hyaline globules. Interstitial fibrosis and tubular atrophy was around 80-90%.

In the setting of collapsing FSGS, endothelial tubuloreticular inclusions should be looked for. Tubulo reticular inclusions are seen in the majority of the cases of HIVAN FSGS than idiopathic FSGS. In our case tubuloreticular inclusions were absent.

In a retrospective study by Salvatore et al (13) of 534 patients with biopsy proven diabetic nephropathy, 26 HIV negative patients were found to have CG superimposed on DN (5% of the total cases). 90% of them presented with nephrotic range proteinuria (mean 9.5g/day) and mean serum creatinine was 3.8mg/dl at the time of biopsy. Extensive arteriosclerosis and arterial hyalinosis were seen in most of the biopsy specimens. (14)

There are no prospective treatment trials of CG. Recent studies have shown remissions in over 50% of the patients treated with cyclosporine and other immunosuppressive agents. (15) Oral corticosteroids are the first line agents followed by cyclosporine if remission not obtained.(16) The roll of MMF in the treatment of FSGS is not yet defined.(17) In addition to immunosuppressive therapy, all patients should be treated with ACE inhibitors or ARB in the attempt to reduce blood pressure, proteinuria and progression to ESRD. Patients with hyperlipidemia will benefit from lipid lowering agents and slower progression of renal failure. (18) Our patient presented with ESRD and he is on weekly thrice hemodialysis now.

Patients with CG are at high risk of progressing to ESRD. Even with the treatment, the incidence of ESRD is 50%-100% in most of the cases. The renal survival of the patients with collapsing FSGS was significantly worse than classic FSGS.(19) Laurinavicius et al(20) used data from 42 patients to determine the factors the determine the progression of CG to ESRD. Male sex, serum creatinine greater than 2.0mg/dl, proteinuria greater than 8gm/day, Interstitial fibrosis and tubular atrophy (IFTA) > 20%, glomeruli with collapsing lesions >20% were associated with the faster progression to ESRD. Our patient presented with the serum creatinine of 7mg/dl, IFTA 70-90% and spot UPCR 8mg/gm. Above all were poor prognostic factors.

Conclusion

As the association between diabetic nephropathy and CG is increasingly being recognized, it is essential to do renal biopsy in all diabetic patients presenting with nephrotic proteinuria or sudden deterioration in renal function of unexplained cause.

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