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CASE REPORT

Acquired Mitochondrial Disease in Type 2 Diabetes Mellitus: A Case Report and Review of Literature

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Abstract

Background: The association of Per-hilar FSGS with type 2 diabetes is not uncommon and represent a form of podocytopathy. Nephropathy in diabetic patients is not content in diabetic nephropathy and various primary glomerulonephritis have been reported. The trend of aggressive urinary abnormalities with rapid deterioration in renal function raises the possibility of nondiabetic renal disease. The association of podocytopathy in the form of heavy proteinuria, muscle weakness and arteriolopathy suggest mitochondrial cytopathy.

Case: We report a 60-year-old male patient with type 2 diabetes presented with typical picture of nephrotic syndrome with high serum creatinine, nephrotic range proteinuria, low serum albumin, high serum cholesterol, anaemia of chronic disease and associated with recurrent cerebral stroke, generalized muscle pain and atrophy in the upper and lower muscle girdle, intermittent air hunger, poor oral nutrition and generalized anasarca with poor response to diuretic therapy. Renal biopsy was done and revealed mesangial sclerosis, minimal change, per-hilar FSGS. Electron microscopy revealed Occasional mitochondria displaying abnormal internal structure. Regular ultrafiltration and haemodialysis was initiated. Improvement of the fluid overload was achieved but patient still suffer muscle pain, weakness, and intermittent air hunger. Which improved after L-carnitin and later patient enjoyed normal kidney function and stopped hemodialysis therapy.

Conclusion: Inhere, we report a rare case of podocytopathy associated with advanced diabetic nephropathy in type II DM that suggesting acquired mitochondrial cytopathy.

Keywords

Mitochondrial disease, Podocytopathy, L-carnitine, Acquired tubulopathy

Introduction

The association of Per-hilar FSGS with type 2 diabetes is not uncommon and represent a form of podocytopathy. Several reports have shown various primary glomerulonephritis can be superimposed on diabetic nephropathy. The appearance of urinary abnormalities or deterioration in renal function inconsistent with natural history of diabetic nephropathy raises the possibility of nondiabetic renal disease and should lead to a more detailed evaluation. The association of podocytopathy in the form of heavy proteinuria, muscle weakness and arteriolopathy suggest mitochondrial cytopathy [1].

Case Report

A 60-year-old male patient with type 2 diabetes presented with high serum creatinine 3.5 mg/dl, heavy proteinuria 13.6 gm/day, serum albumin 1.07 gm/dl, high serum cholesterol 288 mg/dl, anaemia of chronic disease HB 8 gm/l, recurrent cerebral stroke, generalized muscle pain and atrophy in the upper and lower muscle girdle, intermittent air hunger, poor oral nutrition and generalized anasarca with poor response

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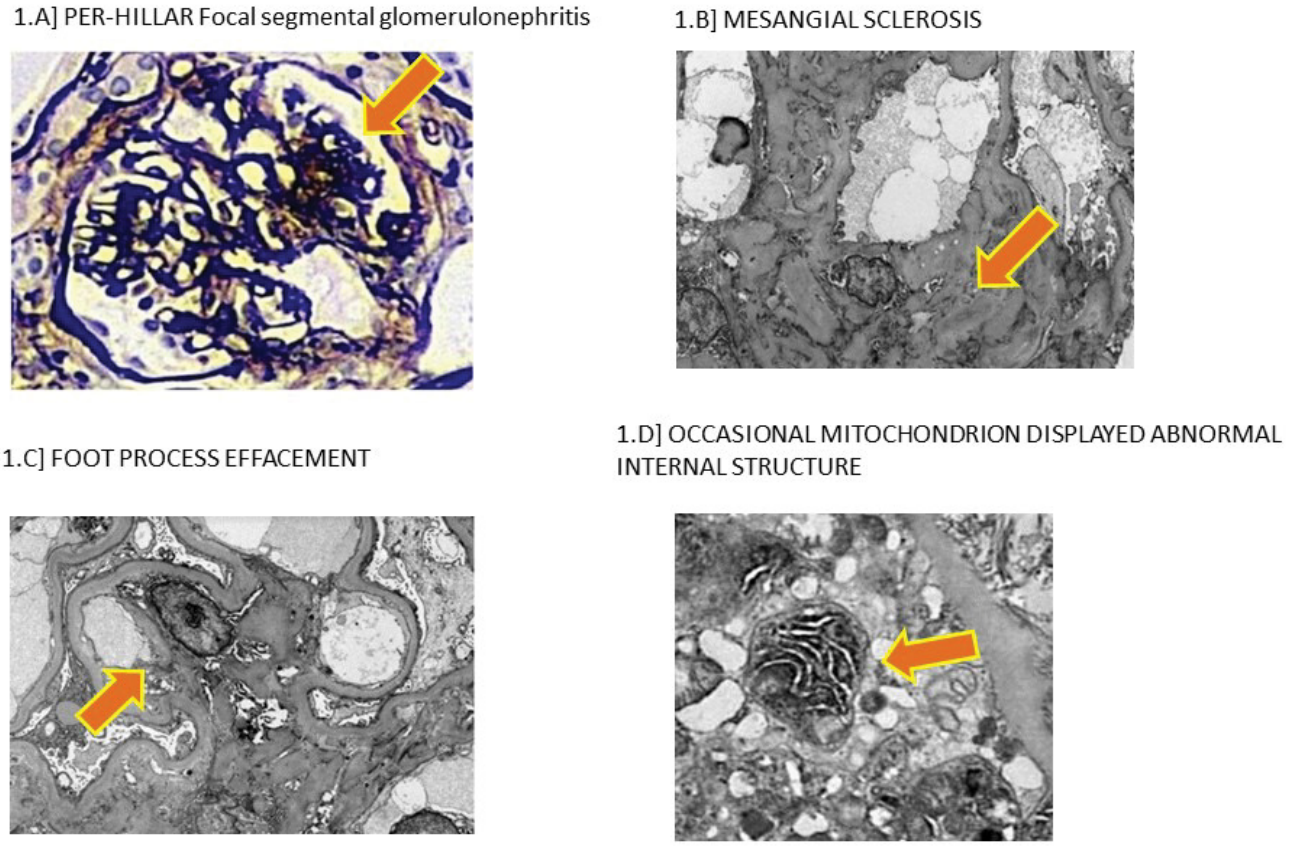

Figure 1: Renal Biopsy Histopathology: A) PER-hillar focal segmental glomerulonephritis, B) Mesangial sclerosis, C) Foot process effacement, and D) Occasional mitochondrion displayed abnormal internal structure.

to diuretic therapy, GFR was 16 ml/min. Renal biopsy was done and revealed per-hilar FSGS (Figure 1A), mesangial sclerosis (Figure 1B). Electron microscopy revealed podocyte foot process effacement (Figure 1C). Carotid doppler showed atherosclerosis with 50% stenosis on the right side and 60% on the left side. In view of refractory anasarca not responding to high dose of diuretic, regular haemodialysis and ultrafiltration was initiated. Improvement of the fluid overload was achieved but patient still suffer muscle pain, weakness, and intermittent air hunger without lung congestion. The clinical presentation was typical for mitochondrial disease which is commonly associated with diabetes, after reviewing the electron microscopy analysis of renal biopsy it revealed mitochondrial structural abnormalities specially in tubular cells confirming the diagnosis of mitochondrial disease (Figure 1D). Genetic analysis to confirm results was not available. L-carnitine was added to improve the mitochondrial metabolism. Patient clinical presentation regarding air hunger improved and started to regain muscle power. Patient serum creatinine and serum albumin were improving (Figure 2) and patient weaned off Renal replacement therapy (haemodialysis) after one year from start of L-carnitine oral therapy and haemodialysis.

Discussion

Diabetic nephropathy is one of the major complications of diabetes and is characterized by abnormal level of albuminuria, decreased in glomerular filtration rate and diabetic glomerular lesion in renal biopsy [1]. It is co-exist in many patients who are diagnosed with type 2 diabetes and can progress and lead end stage renal disease (ESRD) in around 20% of patient with overt diabetic nephropathy [1,2].

Renal biopsy is a diagnostic modality that helps in identifying underlying cause of renal dysfunction. Although not routinely performed in diabetic patients who have abnormal renal function with clinical history that suggest underlying diabetic nephropathy as an underlying cause of progressive renal dysfunction.

We report a case of type 2 diabetic patient, with background history of recurrent cerebral stroke, generalized muscle weakness, sensory-neuronal hearing loss with progressive chronic kidney disease underwent diagnostic renal biopsy and revealed mesangial sclerosis, minimal change, per-hilar FSGS and occasional mitochondria displaying abnormal internal structure.

Focal segmental glomerulosclerosis can be idiopathic and secondary to underlying systemic disease. There are five subtypes of primary FSGS including 1) FSGS not otherwise specified; 2) Per-hilar FSGS; 3) Cellular FSGS; 4) Tip FSGS; and 5) Collapsing FSGS [3].

The finding of underlying muscle weakness and

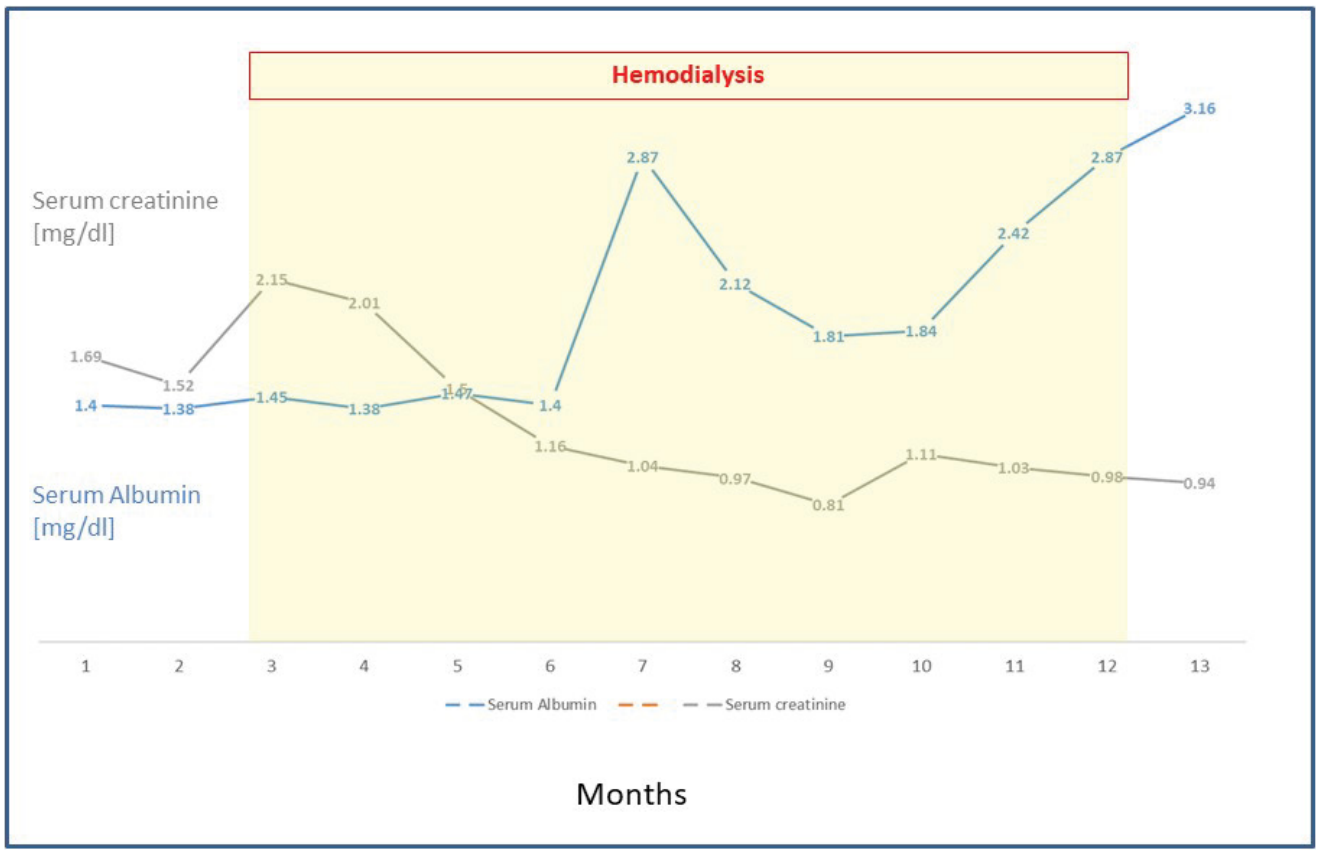

Figure 2: Monitoring of serum creatinine and Albumin: Shows the serial monthly readings of serum creatinine (mg/dl) and serum albumin (mg/dl) in one year time.

atrophy in our patient associated with underlying sensory neuronal hearing deafness and other organ involvement including central nervous system raised the suspicion of underlying mitochondrial cytopathy. For which re-examination of electron microscopy looking for mitochondrial abnormality revealed abnormal mitochondrial internal structures. Mitochondria have essential role in the life and death of cells, and have many important functions, however the most important of which is ATP generation [4].

Clinical manifestation related to mitochondrial disorder is mainly related to defect in oxidative phosphorylation which causes reduction in ATP production and increase ROS production. Theoretically every tissue and organ can be affected by mitochondrial disease, however CNS and skeletal muscle are the most severely affected organs [5].

Mitochondrial dysfunction can result in many renal pathologies and in various forms including tubulopathies, tubulointerstitial nephritis, cystic renal disease or glomerular disease, most commonly focal segmental glomerulosclerosis. With two well defined glomerular disease in patient with mitochondrial cytopathies have been described FSGS resulting from defect in CoQ10 biosynthesis pathway and FSGS secondary to mtDNA 3243 A > G tRNA mutation [6].

Diagnosis of mitochondrial cytopathy is difficult and there are no standardized criteria or accepted guidelines for diagnosis, however combination of different approaches is used to reach the diagnosis. What make it more difficult is that many other systemic disease can mimic or even being secondary cause for mitochondrial dysfunction including diabetes.

Mitochondrial cytopathy with renal involvement is uncommon, however nephrologist should consider it especially in DM patient with deafness as correct diagnosis is essential in choosing the appropriate treatment [7].

Treatment is multidisciplinary team approach, supportive alongside targeted treatment of organ specific complications [8].

Nephrotic syndrome caused by underlying mitochondrial dysfunction mainly due to coenzyme Q deficiency is commonly steroid resistant and treatment required supplementation of Conzyme Q for replacement [9]. Based on clinical findings supported by laboratory and histopathology findings, we have started L-carnitine replacement along with renal replacement therapy. Our patient overtime started to require less sessions of hemodialysis and ended up by improvement of his renal function, and currently is not requiring renal replacement therapy, which support diagnosis of underlying mitochondrial cytopathy being the underlying co-factor for progressive renal impairment.

In conclusion, we are reporting a rare case of podocytopathy associated with type 2 diabetes that suggest acquired mitochondrial cytopathy, improved with L-carnitine therapy.

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