Case Report

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Post-Transplant with Glomerular Lipidosis: A Case Report and a Review of Literature

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ABSTRACT

There is increasing evidence that lipid accumulation in cells and tissues, a process known as lipotoxicity, can lead to dysfunction in multiple organs. Lipid accumulation has also been observed in the kidneys, resulting in glomerular lipidosis. In this report, we highlight a case of a 50-year-old gentleman who developed post-transplant glomerular lipidosis, and accordingly, we explore the treatment options used in his case based on the available literature.

Keywords: Glomerular Lipidosis; Post-Kidney Transplant; Plasmapheresis

Abbreviations: ESKD: End-Stage Kidney Disease; DSA: Donor Specific Antibodies; FCXM: Flow Cytometry Cross Matching; HDL: High-Density Lipoproteins; LCAT: Lecithin Cholesterol Acyltransferase; ACE: Angiotensin Converting Enzyme

Introduction

The data about the effect of Lipid accumulation in various body tissues is expanding rapidly. It may contribute to organ injury via several mechanisms through a process termed lipotoxicity [1]. Renal lipidosis, or lipid deposit in kidney biopsies has been associated with nephrotic syndrome [2]. However, whether excess lipids are the cause, or the consequence of glomerular injuries is not well known. Lipid toxicity is not limited to kidney injuries and has been implicated in a variety of other pathological and physiological conditions [1,3,4]. Cases of glomerular lipidosis have been documented following kidney transplants. In this instance, we present a case of a patient who developed glomerular lipidosis after a kidney transplant but responded well to the available treatments.

Case Presentation

A 50-year-old Saudi male was referred to our transplant center as a potential kidney recipient. The patient had a history of end-stage kidney disease (ESKD), presumably secondary to uncontrolled long-standing diabetes mellitus type II and hypertension. He also had familial dyslipidemia, peripheral vascular disease (status post (S/P) angioplasty of left iliac artery with stenting in June 2016), coronary artery disease (S/P stenting ten years ago, on dual antiplatelet therapy) with preserved ejection fraction. The patient underwent a living emotionally related kidney transplant with a smooth operative course in December 2016. The donor was his wife with 6/6 antigen mismatches, negative T & B Cell Flow cytometry cross-matching (FCXM), and no Donor Specific Antibodies (DSA). He received Basiliximab for

induction and was placed on a triple-maintenance immunosuppression regimen with tacrolimus, mycophenolic acid, and prednisone. He had an uncomplicated postoperative course with immediate graft function, and the serum creatinine improved to 100 -130 umol/liter within a month after transplantation. However, four months after the kidney transplant, the patient was admitted with fever of unknown origin and diagnosed with disseminated tuberculosis (TB) affecting his posterior mediastinal, esophagus, and ascetic fluid. For this, he was treated with anti-TB medications and minimized immunosuppression (mycophenolate was discontinued) for one year.

Serum creatinine maintained stable around 100-120 umol/liter with an albumin-creatinine ratio (ACR) of < 30 mg/gm. His hospital course was further complicated by intestinal obstruction, for which he underwent exploratory laparotomy with adhesiolysis. Early in 2018, his serum creatinine started to trend up to 170 umol/liter with microscopic hematuria without significant proteinuria of ACR < 30 mg/gm. Therefore, renal biopsy was arranged and revealed 2 of 27 glomeruli globally sclerosed, mild interstitial fibrosis and tubular atrophy (approximately 5-10%), no arteriolar hyalinosis and moderate arterial sclerosis, features of glomerular lipidosis, consistent with familial dyslipidemia (Figures 1 & 2). Histological morphology was primarily consistent with type III hyperlipoproteinemia (Familial Dysbetalipoproteinemia). In addition, there was no evidence of atherosclerosis or acute rejection. Accordingly, the patient was diagnosed with glomerular lipidosis based on renal histology and abnormal lipid profile. Treatment of post-transplant glomerular lipidosis is not well established. Our patient was treated with a combination of lipid-lowering therapies, including a high-dose statin and ezetimibe. His lipid profile at the time of biopsy was cholesterol 9.9 umol/liter, triglycerides 1.89 umol/liter, High-Density Lipoproteins (HDL)-cholesterol 0.18 umol/liter and Low-Density Lipoproteins (LDL)-cholesterol 9.39 umol/liter. He was also managed with five sessions of plasmapheresis along with Evolocumab injection every two weeks. Furthermore, he was kept on diet control, dual antiplatelet agents, optimized glucose control, and angiotensin receptor blockage. Now, it has been almost seven years post-transplant, and the patient has stable coronary artery disease with stable creatinine of 148 umol/liter without significant proteinuria. His last lipid profile included cholesterol 3.8 umol/liter, triglycerides 1.8 umol/liter, HDL-cholesterol 0.03 umol/liter, and LDL-cholesterol 3.2 umol/liter. This case highlights the importance of understanding abnormal lipid metabolism in kidney transplant patients and the effect of controlling lipid profile on graft survival. Early identification and treatment of post-transplant glomerular lipidosis can improve kidney function and prolong graft survival.

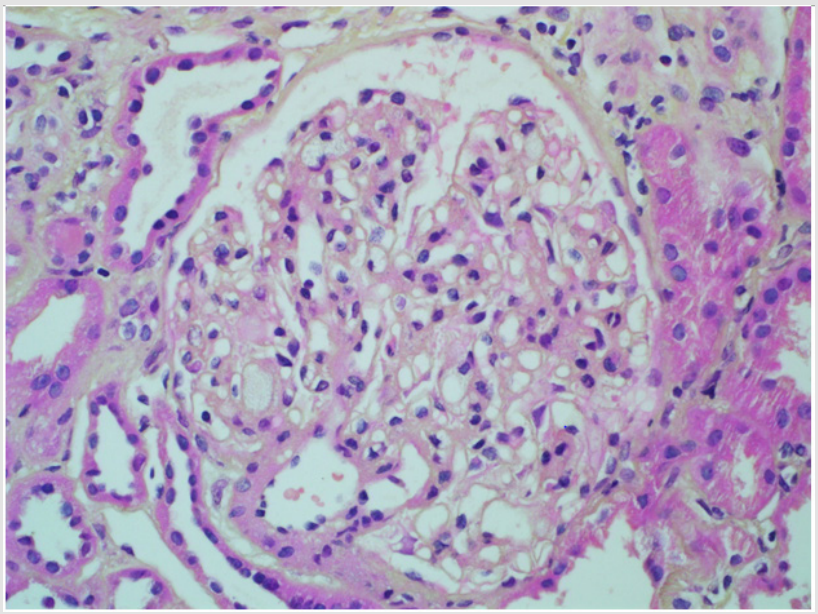

Figure 1: HPS stain shows multiple glomerular capillary loops and mesangial areas filled with foamy macrophages.

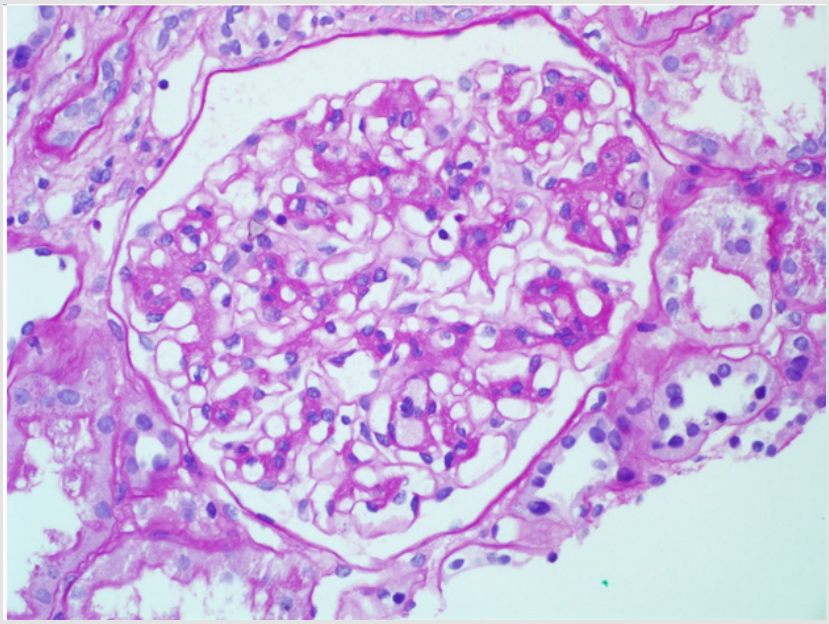

Figure 2: PAS stain shows multiple glomerular capillary loops and mesangial areas filled with foamy macrophages.

Discussion

Lipid abnormalities can present in several renal disorders, such as nephrotic syndrome and its association with hypercholestremia [5]. Inherited abnormal lipid metabolism can also be associated with specific renal lipidosis, such as Fabry disease, Lecithin Cholesterol Acyltransferase (LCAT) deficiency, and von Gierke disease [6]. Moorhead and the associates were first to hypothesize that chronic progressive kidney disease may be mediated by abnormalities of lipid metabolism in 1982. In their hypothesis, they described proposed mechanisms for the pathogenesis of lipid-induced glomerular atherosclerosis and tubulo-interstitial damage in chronic progressive renal disease. After an initial glomerular injury, increased glomerular basement membrane permeability leads to loss of lipoprotein lipase activators, resulting in hyperlipidemia. Circulating low-density lipoprotein binds with glycosaminoglycans in the glomerular basement membrane and increases its permeability. Filtered lipoprotein accumulates in mesangial cells and stimulates them to proliferate and produce excess basement membrane material. Mesangial cell proliferation is a common observation in glomerulonephritis and crescent formation.

Moreover, Lipid droplets are often seen in proximal tubular cells in nephrotic syndrome, and filtered lipoproteins such as High-Density Lipoproteins (HDL) may be altered on passage through the nephron. Penetration of lipoproteins into renal epithelial cells possibly occurs, causing or aggravating tubulo-interstitial disease [7]. Dyslipidemia per se is not sufficient to lead to renal injury but likely contributes to renal injury secondary to different mechanisms. Dyslipidemia may directly affect the kidney by causing renal lipotoxicity and indirectly through systemic inflammation, oxidative stress, vascular injury, and changes in hormones and other signaling molecules with renal action [8]. The available evidence in humans about the link between lipid accumulation and kidney disease is much scarcer compared to animal experiments and trials. Renal lipid accumulation has been described in several contexts, including hypertensive nephrosclerosis, focal segmental glomerulosclerosis, minimal change disease, hepatorenal syndrome, diabetic coma, severe whole-body hypothermia, as well as in rare genetic disorders, including Fabry's disease, familial dysbetalipoproteinemia, Lecithin Cholesterol Acyltransferase (LCAT) deficiency, arteriohepatic dysplasia (Alagille's syndrome), and lipoprotein glomerulopathy (LPG). However, whether renal lipid accumulation is a result of a mediator of renal injury in humans is not known [1,3,4].

Lipid deposition is frequently observed in kidney biopsy specimens, causing glomerular lipidosis. Electron microscopic examination provides interesting findings on the morphological character of lipid depositions. Intraglomerular lipid distribution may be generally classified into four categories—lipid accumulation in the infiltrated macrophages, in the glomerular capillary lumens without foam cells, in the mesangial and/or subendothelial area, and in the glomerular epithelial cells [9]. When reviewing the literature, there are few cases of glomerular lipidosis post-renal transplant. Five cases described the recurrence of lipoprotein glomerulopathy (LPG) post-kidney transplantation, including one who progressed to renal failure within the first year after transplantation [10-14]. Although the treatment and outcome are still controversial, Hu et al., in their retrospective study, demonstrated that fenofibrate-containing treatment improved the lipid profile, proteinuria, and hypoalbuminemia and stabilized

renal function in LPG patients with Apolipoprotein E (APOE) Kyoto mutation. In a 3-year follow-up, fenofibrate significantly delayed the progression of LPG [15]. In the context of renal transplant, two patients with significant proteinuria due to recurrent LPG achieved a reduction in proteinuria with angiotensin-converting enzyme inhibitor therapy [11,13]. In the third case, fenofibrate was used temporarily for four months and replaced with atorvastatin due to an acute rise in serum creatinine [15].

Beyond the context of renal transplantation, ten cases were described and published in the literature about patients with type III hyperlipoproteinemia caused by apolipoprotein E2 (apoE2) homozygotes, a genetic mutation of apoE (Arg158Cys) and leading to glomerulopathy [16].

The primary treatment strategy was through using different lipid-lowering therapies such as statin, fibrate, colestyramine, ezetimibe, and eicosapentaenoic acid, in addition to the use of other approaches such as renin-angiotensin system inhibitors, prednisolone and cyclophosphamide [16-22]. Conversely, repeated plasmapheresis sessions using a dextran sulfate-cellulose column were effective in reducing proteinuria and significantly decreasing both the serum cholesterol and triglyceride in a 59-year-old female with apoE2 homozygote glomerulopathy [17]. Saito [3] on the contrary, have explored various options of therapeutic trials in patients with LPG and stated that the regular treatments of nephrotic syndrome, e.g., steroids, immunosuppressants, and anticoagulants, were ineffective, as well as the lipid-lowering agents were not able to decrease urinary protein and preserve renal function. Additionally, attempts of plasmapheresis or LDL apheresis revealed controversial results, and renal transplantation was performed in four patients; however, all four attempts failed because of the recurrence of LPG [4,5]. Nonetheless, intensive therapy using lipid-lowering agents, including fibrates, was reported to result in clinical remission with histological resolution. In two case studies, the complete disappearance of lipoprotein thrombi was shown in serial renal biopsies, in addition to decreases in serum cholesterol, triglyceride, and apoE levels [4,23,24]. Interestingly, a recent study illustrated a case with nephrotic range proteinuria four months after deceased donor renal transplantation in a patient with end-stage kidney disease (ESKD) presumed secondary to hypertension. The patient had a normal lipid profile, and based upon two transplant kidney biopsies and Apolipoprotein E genotyping, the rare diagnosis of Apolipoprotein E2 homozygosity-related kidney disease post renal transplant was confirmed. The patient was treated with fenofibrate and Angiotensin-Converting Enzyme (ACE) inhibitors with a reduction in proteinuria, and he maintained good, stable kidney function [25]. Since the treatment of post-transplant glomerular lipidosis is not well established, and the therapeutic options are mainly extracted from case reports, we have managed our patient with lipid-lowering therapy as a first-line treatment complemented with five sessions of plasmapheresis in addition to diet control, dual antiplatelet agents, optimized glucose control and angiotensin receptor blockage. He effectively responded to this combination of treatment with stable renal function for seven years.

Conclusion

Lipid abnormalities and lipid accumulation have been implicated in various renal disorders, including nephrotic syndrome and chronic kidney disease. The mechanisms by which lipids contribute to renal injury are complex and involve direct lipotoxicity, inflammation, oxidative stress, and vascular injury. While the available evidence in humans is limited compared to animal studies, there is growing recognition of the importance of lipid management in kidney disease. Various therapeutic approaches have been explored, including lipid-lowering agents, plasmapheresis, and renin-angiotensin system inhibitors. The optimal treatment strategy for post-transplant glomerular lipidosis remains to be determined, but a combination of lipid-lowering therapy, plasmapheresis, and other supportive measures may be effective in stabilizing renal function.

Conflict of Interest

The authors have no conflicts of interest to disclose regarding this case report, its authorship, or its publication.

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