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Case Report

A Case of Podocytic Infolding Glomerulopathy with Diabetes Mellitus, Nephrotic Range Proteinuria and Positive Anti-PLA2R in Serum

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Abstract

Podocytic Infolding Glomerulopathy (PIG) is a new rare pathological entity characterized by invagination of the podocyte cell membrane into the glomerular basement membrane in the kidney biopsy. Discovered over a decade ago, PIG is a podocytopathy detected by electron microscopy that is still unclear as to which autoimmune, hereditary or acquired diseases it is most closely associated with. We report histopathologic findings typical of PIG in a diabetic patient with nephrotic range proteinuria and phospholipase A2 receptor antibodies title found in serum. He was conservatively treated with ACEis and responded with mild decrease in proteinuria.

Keywords: Diabetic nephropathy; PLA2R; Podocytic infolding glomerulopathy

Introduction

Podocytic infolding glomerulopathy is a rare glomerular abnormality which was first proposed as a new disease entity in 2008 [1]. It is characterized by Glomerular Basement Membrane (GBM) bubbling viewable by light microscopy, due to extensive trapping of podocytic cytoplasm fragments and cell membrane projections within the GBM. Electron microscopy reveals infolding of the cytoplasm of the podocytes into the GBM. Most of the cases reported worldwide, indicate that PIG usually co-exists with another autoimmune disease [2,3]. In this case we present a diabetic patient with no other autoimmune disease in his medical history, whose biopsy was characterized as PIG.

Case Presentation

A 60-year-old Caucasian man with a 5-year history of type II diabetes mellitus, hyperlipidemia, hypertension, hyperuricemia, benign colon polyps, was noted by his family physician to have proteinuria and was referred to the nephrologist. He was an active smoker and had been treated with an angiotensin II receptor blocker combined with calcium channel blocker, an SGLT2-inhibitor, a statin, acetylsalicylic acid and allopurinol for 5 years and he was well regulated. He denied any history of allergies, other infections, associated symptoms, or symptoms suggestive of an autoimmune disease. On physical examination, his blood pressure was 100/60mmHg, body temperature, 36.8 ℃, heart rate 80 beats per min; respiratory rate 18 breaths per min, he weighted 102kg, his height was 1.84m and his BMI was calculated at 29.9. There was no low extremity edema, no rash, no arthritis and he had no palpable lymph nodes.

At the point of admission, 24-h urine collection showed 4,5gr of urine protein. His creatinine at the time was normal, an estimated glomerular function rate (eGFR) >90 mL/min/1.73m^2, no hypoalbuminemia or deregulation of hyperlipidemia was noted except for a persistent hypertriglyceridemia. His fundoscopy at this point had no diabetic lesions but cataract was diagnosed. In the immunological work up, there were found normal values of autoantibodies ANA, anti-dsDNA, anti-ENA, complement screening C3, C4, serum and urine protein electrophoresis - immunofixation. He also had negative hepatitis serology. Everything was within normal limits except from serum autoantibodies to Phospholipase A2 Receptor of podocytes which was tested with ELISA and valued 35 RU/mL (<20RU/mL). The ultrasound of the abdomen was also unremarkable. the following 9 months his proteinuria remained at the same levels. Due to the persistent nephrotic range proteinuria (>3.5gr/24h) a kidney biopsy was performed (Table 1, Figure 1).

Test	Results
Hemoglobin, g/dL	14,8 (normal: 13.5-17)
White blood cells, per μL	7.340 (normal: 4,500-9,000)
Platelets x10^{3}μL	168.000 (normal: 150-450)
Sodium, mEq/L	139 (normal: 150-450)
Potassium, mEq/L	4.7 (normal: 135-145)
Urea, mg/dL	56 (normal: 15-50)
Creatinine, mg/dL	1.07 (normal: 0.6-1.3)
Albumin, g/dL	4.9 (normal: 3.5-4.5)
Total cholesterol mg/dl	122 (normal <200)
HDL mg/dl	28 (normal >50)
LDL mg/dl	58 (normal <130)
Triglycerides mg/dl	291 (normal <150)
ANA	negative
ANCA	negative
Anti-double stranded DNA antibody	negative
Anti-ENA	negative
C3, mg/dL	119
C4, mg/dL	25.9
Hepatitis serologies (HbAg, HBsAg,	negative
HBcAb, anti-HCV)	
Anti-PLA2R antibody RU/ml	35 (<20RU/mL)
24-h urine protein mg/24h	4.5
Serum electrophoresis and immunofixation	negative
Serum electrophoresis and immunofixation	negative

ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; HBsAg, hepatitis B surface antigen; HBcAb, antibody to hepatitis B core antigen; PLA2r, phospholipid A2 receptor; C3, complement 3; C4, complement 4.

Table: Patient's blood tests results.

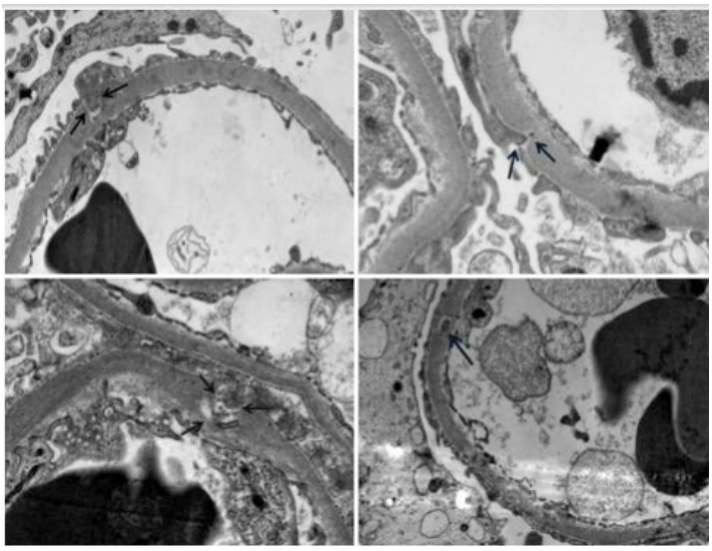

Figure 1: Electron microscopy, arrow pointing the podocytic cytoplasmic processes invaginating into the GBMs.

Renal Biopsy

The renal biopsy was evaluated under light microscope (histochemistry for Congo-Red and immunohistochemistry for C4d, PLA2R and DNAJB9 included), immunofluorescence and electron microscope. The biopsy sample included eight glomeruli, 3 of them globally sclerosed (37.5%), the rest enlarged with mild to moderate mesangial matrix increase and thickening of the GBMs, without spikes, pin holes or reduplications. Immunohistochemistry for C4d, PLA2R and DNAJB9 was negative. Immunofluorescence revealed nothing noticeable (no staining of IgG, IgA, IgM, C3, C1q, C4, κ-λ chains) apart from a moderate linear albumin staining. Without electron microscopy the whole picture was rather reminiscent of mild to moderate lesions of diabetic nephropathy.

One glomerulus was available for evaluation by electron microscopy. A moderate increase in mesangial substance, segmental compact mild to moderate thickening of the capillary walls, without classical electron-dense deposits were found. Effacement of podocytes' foot processes was multi-segmental. More importantly, podocytic cytoplasmic processes invaginating into the GBMs were

observed, accompanied by scattered endomembranous, partially microspherular microstructures, sometimes with adjacent unclear small pyknotic areas. The biopsy report concluded that although light microscopy and immunofluorescence findings could indicate diabetic nephropathy, the electron microscopy lesions suggest the diagnosis of PIG.

Discussion

PIG is a newly described glomerulopathy which was proposed as a disease entity in 2008. Using the electron microscopy, PIG has been categorized into three classes based on the typical changes in the glomerular basement membrane (GBM). Class A is characterized by primarily podocyte infolding only; class B contains microstructures in the GBM and primary podocyte infolding, whereas class C is defined only by the presence of microstructures in the GBM [4,5]. It seems that in those 44 cases of PIG that have been reported globally, an autoimmune disease coexists PIG presents great heterogeneity in terms of coexisting diseases, immunological profile and histopathological pattern. Most of the reported comorbidities are connective tissue diseases, mainly systemic lupus erythematosus. Other connective tissue diseases, such as rheumatoid arthritis, primary biliary cirrhosis, mixed connective tissue disease, and Sjogren syndrome have been announced in combination with PIG [3,6,7]. In some cases, there was a co-existing viral infection and in other cases hydronephrosis was reported [8,9]. Focal segmental glomerulosclerosis (FSGS) and Membranous nephropathy (MN) are the two most common glomerulopathies that have been associated with PIG in case series [10].

The extent to which PIG is related to the presence of circulating antibodies against PLA2R receptor is currently under observation. More or less 70 to 80 percent of patients diagnosed with primary MN have a positive test (ELISA and/or IFA) [11]. A small percentage of patients with secondary MN will have a positive test for anti-PLA2R antibody; some of these patients may actually have primary MN with superimposed but unrelated infection, cancer, autoimmune disease or use of medication. The anti-PLA2R existence in the serum is highly suggestive of primary MN, but does not exclude the coexistence of other conditions such as: infection, malignancy, or another inflammatory disease [12,13]. Patients diagnosed with nephrotic syndrome without MN in kidney biopsy hardly ever have a positive test for the anti-PLA2R antibody. Rare cases have been reported with nephrotic syndrome with a positive ELISA for anti-PLA2R and a pathological diagnosis other than MN [14].

As far as treatment is concerned, there have been several therapeutic strategies followed by the clinicians in order to deal with the peculiar new glomerulopathy of PIG. Retrospectively, clinical outcomes of PIG in most cases were quite good. The immunosuppressive regiments used mainly consisted of corticosteroids, rituximab, cyclosporine, cyclophosphamide and tacrolimus [5,15]. Some patients also received only supportive conservative treatment and had achieved complete or partial response. It seems that PIG is relatively benign and clinicians should not be afraid to face this new disease entity.

Conclusion

To our knowledge, this is the first reported case with PIG and anti-PLA2R antibodies detected in the serum, without clear histological evidence of membranous nephropathy. Our patient was diabetic for five years with no diabetic lesions in fundoscopy. Although PIG has been reported mainly in the context of autoimmune diseases, the coexistence with diabetes or its possible role in PIG's pathogenesis has not been addressed. The treatment of this peculiar morphologically disease, still remains an open query for physicians.

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