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Case Report

Establishing the Cause of Nephrotic Syndrome in an Unlikely Scenario – A Case Report

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Abstract: Chronic hyperglycemia in the context of type 2 diabetes predisposes patients to developing diabetic chronic kidney disease. The following clinical case covers a 55-year-old patient with a longstanding history of type 2 diabetes and essential hypertension admitted for typical symptoms of uncontrolled diabetes to the Diabetes Department of "Pius Brinzeu" Emergency Hospital. Clinical evaluation and laboratory results pointed to the diagnosis of nephrotic syndrome, however, did not present at first a clear cause for such high levels of proteinuria. This report follows the meticulous logic needed in order to establish the cause of nephrotic syndrome, all the way to a justifiable renal biopsy. Once diabetic nephropathy was established, adding treatment with an SGLT2i was considered a valid treatment option due to its antiproteinuric effects.

Keywords: empagliflozin; nephrotic syndrome; type 2 diabetes

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Introduction

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) currently represent one of the most used lines of therapy in treating patients with type 2 diabetes [1]. Their main mechanism of blood glucose reduction is blocking glucose reabsorption in the proximal tubules in the nephron increasing urinary glucose excretion [2]. Beyond glycemic management, these medications also assist in weight loss, lower blood pressure, prevent major cardiovascular events, and slow the progression of chronic kidney disease (CKD) [3,4]. Nephrotic syndrome is defined by nephrotic range proteinuria (≥3500 mg/24 hours), edema,

hypoalbuminemia, and hyperlipidemia [5]. Empagliflozin was linked in the EMPA-REG OUTCOME trial to a 50% decrease in the composite kidney outcome of renal mortality, kidney replacement therapy, or doubling of serum creatinine in patients with nephrotic range proteinuria, with no difference when compared to those without nephrotic range proteinuria [6]. The mechanisms behind the nephroprotective effects of SGLT-2 inhibitors have been the subject of several hypotheses. These include decreased renal hyperfiltration through tubule-glomerular feedback, decreased sodium reabsorption in proximal tubules, decreased energy consumption by proximal tubular cells, protection of proximal tubular cells from glucotoxicity, improved mitochondrial function, decreased oxidative stress, increased erythropoiesis, decreased autophagy, podocyte damage, and renal inflammation [4].

Case presentation

A 55-year-old male patient with type 2 diabetes was referred to the Department of Diabetes, of the "Pius Brinzeu" Emergency Hospital Timisoara, with polyuria, polydipsia, and signs of dehydration. The patient was diagnosed with type 2 diabetes in 2007, having clear clinical features of type 2 diabetes (abdominal obesity, high blood pressure). Since glycemic control could not be achieved through oral antidiabetic agents alone, and because the patient presented digestive intolerance to metformin, treatment with insulin was started within a year of the diagnosis.

On admission to the Diabetes Department in 2022, the patient was undergoing treatment with regular insulin 10 units before breakfast and lunch and premixed insulin (30% regular insulin/70% insulin-NPH) 14 units before dinner. The patient also presented a personal history of essential hypertension and secondary hypertriglyceridemia. The patient history is summarized in Table 1.

Table 1: Medical history, baseline treatment and treatment changes after diagnosis.

Medical history	Baseline treatment	Start/end dates	Switch to other treatments
2007: Type 2 diabetes	Metformin 1 g b.i.d	2007/2008	Switch to human insulin
	Regular insulin: 10 UI-10 UI-0 UI; Premixed insulin (30% regular/70% NPH) 0 UI-0 UI-14 UI	2008/2022	
2007: Esential hypertension	Candesartan 16 mg b.i.d Indapamid 1.5 mg q.d.	2007 onward	
2007: Secondary hypertriglyceridemia	Rosuvastatin 10 mg q.d.	2007 onward	

Upon admission, the patient was examined and evaluated for glucose and lipid control and underwent screening for the chronic complications of diabetes. The fundus exam showed no modifications consistent with diabetic retinopathy, while the neuropathy tests showed diminished vibratory and tactile sensibility, ankle brachial index: left lower limb = 1; right lower limb = 0.99. The clinical and lab values of the patient are presented in Table 2.

Table 2: Clinical and laboratory parameters

Parameters	2007	2022
BMI (kg/m^2)	30	34
Blood pressure (mmHg)	180/80	140/75
HbA1c (%)	7.55	7.4
Creatinine (mg/dl)	1	1.1
eGFR (ml/min/1.73 m^2)	98	79
UACR (mg/g)	-	995
LDLc (mg/dl)	-	35
Triglycerides (mg/dl)	225	315

UACR= urinary albumin-to-creatinine ratio

Considering the particularly high UARC value, 24 h proteinuria was measured, and a diagnosis of nephrotic syndrome was established, as the value was 4.7 g/24 h. Due to the complexity of the case, an interdisciplinary team comprising a diabetologist and a nephrologist has continued the clinical management of the patient. The next step was to establish the etiology of the nephrotic syndrome. Since the fundus exam showed no modifications consistent with diabetic retinopathy, diabetic nephropathy was considered to be an unlikely cause, and further confirmatory tests were ordered. As the patient presented a long history of essential hypertension an echocardiography was performed, showing: left ventricular hypertrophy, type 1 diastolic disfunction, and a preserved ejection fraction of the left ventricle of 50%. Immunological and oncological causes were also considered and a battery of tests comprising tumor markers, immune-electrophoresis, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-phospholipase A2 receptor antibodies, IgA, IgG, IgM, C3, were ordered, all being within the normal range. Further imaging tests were also ordered; however, the CT scan presented no modifications that could elucidate the cause of the nephrotic syndrome.

At this point, a renal biopsy was done in order to establish the root cause of the nephrotic syndrome. Histopathological examinations of the biopsy samples were performed using hematoxylin-eosin, periodic acid-Schiff, periodic Schiff-methenamine, trichrome and Congo red staining, respectively. Microscopy revealed nodular and diffuse expansion of the mesangial matrix as well as Kimmelstiel-Wilson nodules. Against all odds, these pathognomonic modifications have helped to establish the diagnosis of diabetic nephropathy.

In order to enforce glucose control, the insulin regimen was adapted to basal-bolus therapy using insulin glargine (44 U/day) and insulin aspart (18 units before breakfast, 16 units before lunch, and 10 units before dinner). After achieving glucose control, the question remained as to what could be used to reduce proteinuria in this case. The chosen therapeutic drug was empagliflozin, a SGLT2i, known to diminish urinary protein output. The subsequent evolution of the clinical and laboratory parameters of the patient is presented in Table 3.

Table 3: Evolution of clinical and laboratory parameters

Parameters	**2022**	**2023**
BMI (kg/m^2)	34	34
Blood pressure (mmHg)	140/75	125/70
HbA1c (%)	7.4	7.2
Creatinine (mg/dl)	1.1	1.1
eGFR (ml/min/1.73 m^2)	79	79
24h proteinuria (g/24h)	4.7	2.2

Discussion

What is truly particular about this case is the fact that, even though the patient presented a long history of uncontrolled diabetes, which could suggest that this could be the cause of proteinuria, there was a discrepancy between the severity of microangiopathy in the kidneys leading to nephrotic levels of proteinuria, and the lack of lesions in the retina upon eye fundus examination.

Prolonged exposure to high glucose values in patients with type 2 diabetes leads to microvascular complications such as diabetic nephropathy and diabetic retinopathy [7]. According to the American Diabetes Association, individuals with diabetes who have chronic kidney disease typically exhibit retinopathy, albuminuria without significant hematuria, and a progressive decrease of eGFR [8]. Other authors have described similar situations in which diabetic nephropathy was present in the absence of retinopathy, the explanation being that even though part of their pathogeny is similar, the kidneys and the eyes have different internal structures leading to a difference in response to diabetes-induced microvascular damage, causing a nonparallel evolution of the disease in some cases [9]. In our presented case there was a similar unparallel evolution of diabetic microangiopathy in the sense that the kidneys presented with more

severe damage through nephrotic levels of proteinuria while the eye fundus examination was still normal. In contrast in a retrospective study, authors have shown that in patients with diabetic nephropathy, without diabetic retinopathy have less severe renal damage, while also suggesting that in such cases renal biopsy is significant in diagnosing the cause of the renal damage [10].

In a recently published pro/con review article by Zoccali et al, the need for renal biopsies in diabetic patients it is justified, as renal biopsies may identify atypical features, help differentiate from systemic diseases with renal impact, and target immunotherapy. The individualized decision of performing a renal biopsy in diabetic patients should rely, according to the authors, on the presence of hematuria, sudden-onset proteinuria and the rapid decline of renal function, as well as a short duration (<5 years) of diabetes and the lack of retinopathy [11].

Establishing the cause of the nephrotic syndrome is essential for the proper management of the patient. In most cases, this is achieved following a meticulous exclusion algorithm encompassing metabolic, immunologic and viral causes, with renal biopsy providing certainty, if needed [12,13]. To confirm this algorithm, Kwon et al have organized the Renal Biopsy Epidemiology Project with 242 patients with a history of diabetes. Even though there was a selection bias, and renal biopsies were not done in a protocolized manner, only 37.2% of the patients had diabetic kidney disease alone. Other frequent findings were focal segmental glomerulosclerosis, IgA nephropathy, ANCA vasculitis and membranous nephropathy. Bearing in mind the potential treatment for these concomitant diseases, it is relevant to have a diagnosis of certitude. The risk factors identified in this study associated with additional findings on the renal biopsy were: Hba1C <7%, the absence of diabetic retinopathy, a protein/creatinine ratio of <3 mg/g, and a urinary albumin/creatinine ratio <300 mg/g [14].

Around 20% to 30% of patients with type 2 diabetes will develop some degree of diabetic kidney disease throughout their lives, while 3% of patients present overt nephropathy at diagnosis. Onset of nephropathy usually starts with glomerular hyperfiltration, continuing to overt proteinuria, and leading to fully-fledged proteinuria [15,16]. While originally intended as a glucose lowering medication, empagliflozin has shown versatility in treating a larger spectrum of diseases, targeting a variety of pathological mechanisms, including proteinuria [4,6,8]. Interestingly, the magnitude of proteinuria reduction has succeeded in achieving normal ranges in this case. A recent retrospective study provides evidence suggesting that SGLT2i could be used to reduce proteinuria by more than 30% [17].

Conclusions

Meticulous algorithmic thinking should be used when managing cases with uncertain underlying causes. Antidiabetic medications from the newer generations could provide a valid treatment option in the integrated management of the nephrotic syndrome.

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