Deciphering the Complexity: Nephrotic Syndrome in Autosomal Dominant Polycystic Kidney Disease – A Case Report and Literature Review

Nefrologo in corsia

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ABSTRACT
Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a genetic disorder characterized by the development of multiple renal cysts and the growth of total kidney volume, often leading to progressive kidney failure. While glomerulonephritis is potentially recognized as a complication, the presence of glomerulonephritis among ADPKD patients is considered uncommon, and the incidence of nephrotic syndrome within this population is exceptionally rare.
We present a case of a young woman with ADPKD who developed nephrotic syndrome, likely due to minimal change disease. The diagnostic challenges, management strategies, and existing literature on this rare association are here comprehensively reviewed.

KEYWORDS: Autosomal Dominant Polycystic Kidney Disease, nephrotic syndrome, renal biopsy, MCD, case report

Introduction

ADPKD is a genetic disorder characterized by the formation of renal cysts, culminating in renal enlargement and dysfunction. ADPKD is the fourth leading cause of ESKD [1]. Among the clinical manifestations of ADPKD, urinary alteration is unusual. Typically, proteinuria when present is < 1 g/die and urinary sediment is generally inactive. Although glomerulonephritis can complicate ADPKD, the concurrent presentation of nephrotic syndrome, especially MCD, is quite exceptional [2, 3]. Thus, the occurrence of nephrotic proteinuria in the course of ADPKD is very rare. In these situations, the clinicians have to decide to run the risk of a kidney biopsy or attempt to make the diagnosis through clinical and immunological tests.

The decision to conduct a biopsy in ADPKD patients depends on factors like safety considerations and whether obtaining tissue diagnosis would impact treatment decisions.

Among complication rates after kidney biopsy, bleeding is the most common clinically significant event (70% of patients) [4]. In the systemic review of Corapi [5], also, macroscopic hematuria was observed in 3.5% (95% confidence intervals: 2.2–5.1%), blood transfusion in 0.9% (0.4–1.5%), angiographic intervention in 0.6% (0.4–0.8%), nephrectomy in 0.01% and death in 0.02%.

In patients suffering from ADPKD all these risks are increased depending on the progression of the disease and the number of cysts due to the risk of rupture.

In situations where a biopsy is deemed necessary open renal biopsy is typically carried out for individuals with ADPKD. However, novel approaches have been described for use in “high-risk” settings where conventional contraindications to kidney biopsy exist. Alternative approaches such as open surgery, transvenous methods (like trans-jugular or trans-femoral), laparoscopy, or transurethral methods are also possible options [6].

The literature indicates that, in the general adult population, membranous nephropathy (MN) is the most prevalent form of idiopathic nephrotic syndrome, followed in frequency by minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). Approximately 30% of nephrotic syndrome cases in adults may be associated with underlying systemic conditions such as diabetes mellitus, amyloidosis, or systemic lupus erythematosus. Similarly, MN and FSGS are the most common primary pathological lesions observed in adult patients with nephrotic syndrome and coexisting ADPKD. However, the literature also reports other pathological types, including mesangial proliferative glomerulonephritis, IgA nephropathy, amyloidosis, crescentic glomerulonephritis, diabetic nephropathy, lupus nephritis, and post-infectious mesangial proliferative glomerulonephritis [7].

In a literature review of 1995 [8], 22 patients with ADPKD and nephrotic syndrome were identified and 14 received kidney biopsy exhibiting various histological diagnoses including focal glomerular sclerosis, minimal change disease, membranous nephropathy, and IgA nephropathy. A more recent review in 2010 [9] found only a few new cases of nephrotic syndrome associated with ADPKD in adults in addition to those reported in the previous literature revision. We have collected all cases of ADPKD and nephrotic syndrome published since 2000.

FSGS appears to be more frequent in ADPKD, likely due to maladaptive mechanisms driven by early-onset glomerular hyperfiltration, often starting in childhood. Although the precise pathways through which glomerular hyperfiltration leads to segmental scarring and renal function decline are not fully understood, studies suggest that a reduction in renal mass triggers intrarenal vasodilation, increased glomerular capillary pressure, and enhanced plasma flow per nephron [6, 8]. This compensatory hyperfiltration initially maintains GFR but also causes glomerular enlargement, with expansion of matrix components and increased endothelial and mesangial cells [10].

The process of diagnosing glomerulonephritis in ADPKD patients typically involves assessment along with evaluation of the urinalysis in quantitative terms of proteinuria with the respective electrophoresis of urinary proteins (selective or non-selective glomerular proteinuria) and blood tests.

Diagnostic tests for glomerulonephritis in ADPKD patients certainly include, as in the workup of any glomerular disease, urine sediment examination. The presence of dysmorphic erythrocytes and/or erythrocyte casts suggests a glomerular disease, and particularly a proliferative form of glomerulonephritis. However, the sensitivity and specificity of this test alone may not be sufficient for a definitive diagnosis and are often used in conjunction with other immunological and clinical measures.

Furthermore, while not a direct test for glomerulonephritis, genetic testing for ADPKD may be performed to confirm the diagnosis of ADPKD, which can help in understanding the patient's overall kidney health and potential complications [1]. Actually, in ADPKD prognosis differs by genetic mutation, with PKD1 mutations typically indicating earlier onset and more aggressive disease progression compared to PKD2 mutations [11].

The first report of a case of ADPKD and minimal change disease was done in 1991 by Nakahama et al. [12]. Minimal change disease (MCD) is commonly a major cause of nephrotic syndrome, particularly in children in whom it accounts for approximately 90% of cases. The exact cause of MCD is not well understood, but it is believed to involve T-cell-related mechanisms [13]. However, several potential pathways that result in podocyte activation and proteinuria have been identified, such as some drugs, malignancies including Hodgkin disease, mycosis fungoides, chronic lymphocytic leukemia, or secondary allergic forms (pollens, house dust, insect stings). In 2022 a study by Watts et al. [14] discovered nephrin autoantibodies in a subset of adults and children with minimal change disease. A recent study of August 2024 by Hengel et al. [15] confirms that the circulating antinephrin autoantibodies were common in patients with minimal change disease or idiopathic nephrotic syndrome and appeared to be markers of disease activity and provides further support for an autoimmune etiology.

The estimated incidence ranges from 2 to 7 new cases per 100,000 children. While the exact prevalence remains uncertain it is approximately estimated to be between 10 and 50 cases per 100,000 children [9]. MCD is uncommon in adults, and the precise occurrence is undetermined. In preadolescents, MCD makes up 85-95% of all cases of nephrotic syndrome, while in adolescents and young adults the prevalence is 50%, and in adults MCD accounts for 10-15% of primary nephrotic syndrome cases. Corticosteroid treatment is usually effective in inducing remission, but relapse is common and repeated therapy is often required. Among children with MCD, 25% never relapse, 25% relapse infrequently, and 50% have numerous relapses [16].

While there are anecdotal case reports of ADPKD associated with nephrotic syndrome, including MCD, the prevalence of such associations is extremely low [2, 17].

In this paper, we present a case of a young woman with ADPKD who developed nephrotic syndrome, likely due to MCD, highlighting the importance of vigilance for glomerular involvement in ADPKD patients presenting with nephrotic-range proteinuria. Timely diagnosis and personalized treatment are essential for optimizing outcomes in such rare occurrences.

First author	Age	Sex	Kidney Biopsy	Diagnosis	Therapy	Outcome
Ekaterini et al. [9]	9	M	No	–	CS (oral)	Remission
Savaj et al. [18]	29	M	Yes	FSGS	CS + cyclosporine	Remission
Peces et al. [19]	38	M	Yes	MN	1. CS 2. CS + Chlorambucil 3. CS + MFM	1. Resistence 2. Partial remission for ten months 3. Remission
Hiura et al. [20]	70	M	Yes	IgAN	CS	Remission
Sar et al. [21]	39	M	No	Amyloidosis secondary TBC	Colchicine + TBC terapy	N/A
Akinbodewa et al. [22]	24	F	Yes	SLE stage II	Prednisolone + MFM	Remission
D'Cruz et al. [23]	35	M	Yes	D-PGN	Conservative	Partial remission
Visciano B et al. [2]	26	M	Yes	MPGN	CS (oral)	Remission
Yenigun et al. [24]	52	M	Yes	Amyloidosis	Colchicine	Started hemodialysis
Oda Y et al. [25]	23	M	Yes	FSGS	Conservative	Started hemodialysis

Table 1. Cases of nephrotic syndrome related to ADPKD since 2000. MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MN: membranous nephropathy; IgAN: IgA nephropathy; D-PGN: diffuse proliferative glomerulonephritis; SLE: Systemic lupus erythematosus; MPGN: mesangial proliferative glomerulonephritis. N/A: Data not available. mycophenolate mofetil (MFM).

Case report

A 52-year-old woman with a medical history notable for allergies to NSAIDs, dust mites, cypress pollen, and cat dander. The patient's mother is alive and has hemophilia A, while the father is affected by autosomal dominant polycystic kidney disease. Remarkably, the patient herself is a carrier of hemophilia A, inherited maternally.

At the age of 20, diagnosis of ADPKD was made based on familial history, with Ravin and Pei ultrasound criteria being met. Genetic testing revealed an intronic mutation in PKD2. The patient has never experienced gross hematuria, abdominal pain, or renal infections.

At the age of 40, hypertension was first diagnosed, and treatment with an angiotensin receptor blocker was initiated with beneficial effects. At 42 years old, in September 2014, the patient developed nephrotic syndrome characterized by weight gain, proteinuria of 6 grams in 24 hours, and severe hypoalbuminemia, despite normal renal function. Immunologic screening was negative, including PLA2R and sUPAR. Urinary sediment examination was inactive. Secondary oncologic, pharmacologic and infectious causes of glomerulopathy were excluded. Due to the presence of renal polycystic disease with a large cyst (approximately 7 cm) in the left lower renal pole and the high risk of bleeding in a patient with hemophilia A, a renal biopsy was contraindicated. Ex adiuvantibus corticosteroid therapy was initiated with intravenous methylprednisolone of 1 gram day for three consecutive days followed by oral prednisone at 0.5 mg/kg/day. After three months of steroid therapy, proteinuria resolved almost completely (224 mg/24h) with a creatinine level of 0.66 mg/dl. Corticosteroid therapy was then tapered off also due to poor tolerance and different side effects. Three months later, there was a significant recurrence of nephrotic syndrome (urinary protein 14 grams/24h) despite persistence of normal renal function (creatinine 0.6 mg/dl). The response to corticosteroids therapy and the recurrence of NS after its withdrawal suggested a MCD. Due to the inability to use calcineurin inhibitors in ADPKD for their nephrotoxic effects [26], exacerbating renal deterioration, treatment with rituximab was initiated. Following the first administration of rituximab (1 gram), complete remission of the disease was achieved. Two subsequent recurrences of proteinuria occurred following allergic episodes, both of which responded promptly to rituximab

boluses. The last recurrence occurred in 2018, which spontaneously regressed. To date, there have been no further recurrences, with proteinuria within normal limits and normal renal function. The patient is currently followed up at our clinic for genetically determined renal cystic diseases (Figure 1).

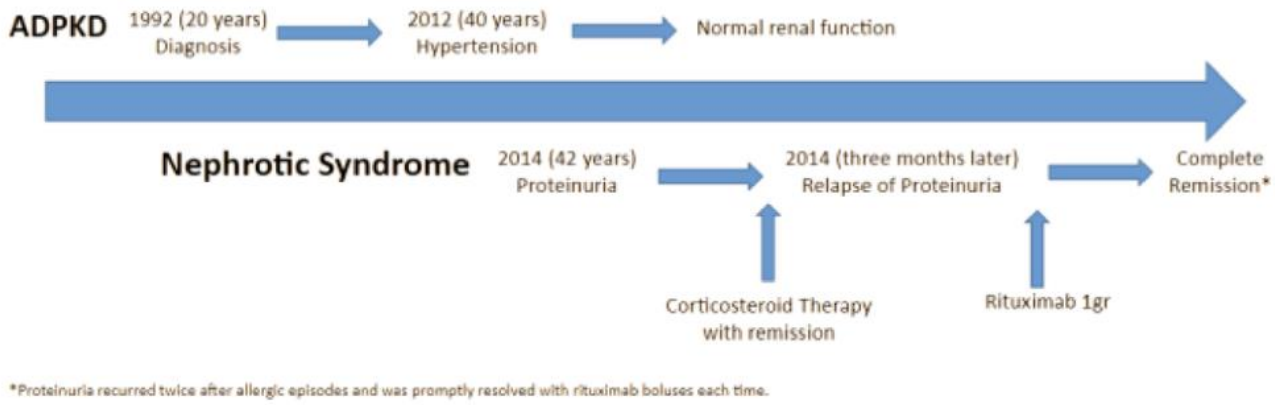

Figure 1. Summary of the patient's clinical history.

Discussion

In our case, the diagnosis of MCD is inherently presumptive yet highly plausible, given the severity of nephrotic syndrome, selective glomerular proteinuria, rapid response to corticosteroids therapy, recurrences post-allergic episodes, and maintained renal function despite significant proteinuria and frequent relapses. The conjunction of nephrotic syndrome, notably MCD, with ADPKD epitomizes a rare clinical phenomenon. Our case underlines the importance of an accurate evaluation of the patient with urinary and blood tests to achieve the best diagnostic hypothesis in the absence of a histological diagnosis. In this regard, new urinary markers such as urinary CD80 have shown great promise in aiding the diagnosis of MCD [27]. Given the complexity of patients suffering from ADPKD, renal biopsy must be evaluated in terms of the risk/benefit ratio, particulary in cases in which there is a lack of response to therapy or in cases of steroid resistance. As previously stated, ADPKD patients face heightened risks with renal biopsy. Indeed, unlike our situation, histological diagnosis is frequently essential, making open renal biopsy pivotal in crafting appropriate treatment strategies due to the diverse glomerular subtypes associated with nephrotic syndrome. Interventions to make renal biopsy more accessible and safer are vital to overcome barriers to precise diagnosis and timely treatment. An appraisal of existing literature highlights the scarcity of reported cases and underscores the exigency for further prompt and decisive actions.

Conclusion

Nephrotic syndrome, attributed to conditions such as MCD, can rarely manifest in ADPKD. It's essential to maintain vigilance for glomerular involvement in ADPKD patients with nephrotic-range proteinuria. A precise diagnosis is imperative to initiate customized treatment for resolution. This approach is critical not only for addressing associated systemic effects like hypercholesterolemia and hypercoagulability but also for slowing the progression of renal failure. In ADPKD patients, already predisposed to chronic renal damage early intervention is particularly crucial. Prompt diagnosis and personalized management are pivotal for optimizing outcomes in these rare instances. Further research efforts are warranted to refine management strategies for this uncommon association.

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