Nephrotic syndrome and autosomal dominant polycystic kidney disease: a report of two cases and literature review

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease characterized by the formation of bilateral renal cysts in addition to multisystem cyst formation like the liver and pancreas. Microalbuminuria and non-nephrotic range proteinuria, is a common finding on routine examination in ADPKD patients; however, the association of frank nephrotic syndrome with ADPKD is rare.

Here, we report two cases of full blown nephrotic syndrome in patients with ADPKD. The diagnosis had been accomplished with ultrasound guided renal biopsy. Histopathology diagnoses were consistent with minimal change disease and membranous glomerulonephritis. We've reviewed the corresponding literature and compared the diagnostic methodology and results.

These two cases and the reviewed literature reports indicate the feasibility and importance of renal biopsy in patients with nephrotic syndrome in the context of ADPKD to have the diagnosis and to guide the best therapy.

Key words: Nephrotic syndrome, and ADPKD.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder characterized by multiple, bilateral renal cysts associated with cysts in other organs, such as liver, pancreas, and arachnoid membranes.[1]

ADPKD is inherited as an autosomal dominant trait with complete penetrance. The autosomal dominant polycystic kidney disease (ADPKD) proteins now known as polycystin-1 and polycystin-2 play a critical role in the normal function of the primary cilium that is essential to maintaining the differentiated phenotype of tubular epithelium. In about 85% of the cases, the disease is caused by a mutation localized on chromosome 16 (PKD1) and in 15% by a mutation localized on chromosome 4 (PKD2), while a few families have been identified in which the disease is caused by a mutation in an unmapped locus. The prevalence of ADPKD estimated to be between one in 400 and one in 1000.[2,3]

In addition to cyst formation, the renal manifestations of ADPKD include hypertension, haematuria, renal stones, recurrent urinary tract infections and cyst haemorrhage. Proteinuria and microalbuminuria also occur with a highly variable severity and are associated with a more progressive course of the disease. Mild proteinuria, usually <2 g/24 h, is a common finding on routine examination in ADPKD patients; however, the association of nephrotic syndrome with ADPKD is considered rare.[4,5]

Here we report two cases of nephrotic range proteinuria and nephrotic syndrome proved by renal biopsy in two patients with ADPKD.

Case 1

A 16 years old female presented with generalized body oedema for four months. Her condition was waxing and waning over five years with partial responses to oral steroids and diuretics. During all presentation her blood pres-

sure as well as renal function were normal. Other systems review were unremarkable. She has a positive family history of death due to ADPKD and end stage renal disease (ESRD) but there was no family history of proteinuric renal disease. On clinical examination she was pale, oedematous, and breathless. Her blood pressure was 160/100 mm Hg and body weight was 77 kg. Her urinary albumin excretion was 10 g/24 hr and serum albumin was 1.2 mg/dl. Urine analysis showed ++ RBCs per high power field. Serum creatinine was 1.07 mg/dl. Her cholesterol was 471 mg/dl and the triglyceride was 319 mg/dl. Chest X-ray revealed bilateral pleural effusion. Immunology and virology testing were negative. Ultrasound imaging and Native CT scan of the abdomen revealed that right kidney measuring 129*51*22mm and the left kidney measuring 123*58*18mm. Both show multiple cysts of variable sizes, with bilateral focal areas of elevated density, the largest in the lower pole in the right kidney measured 1.8cm with possibility of haemorrhage inside the cyst. There was a mid-pole 0.6 cm stone in the left kidney. There was no other cysts in other viscera. Significant ascites noted with generalized subcutaneous oedema.

We started treatment in form of IV antibiotic, antiproteinuric measures in form of ramipril 5 mg/day and diltiazem 90 mg/day plus statins and IV furosemide. We reintroduced steroids intravenously in high dose of 250 mg methylprednisolone /day for three days. The patient started to respond and by the end of the first month her body weight was 57 kg with no edema. Her normal renal function maintained and the daily urinary protein excretion decreased to 1.1 gm/24 hr. At this time, a US-guided biopsy of the left lower pole was performed. The diagnosis was consistent with minimal change disease (MCD). Figure 1

Now we followed the patient for two years and she is on antiproteinuric measures only with creatinine of 1.2 mg/dl and urinary protein of 0.7 gm/24 hr.

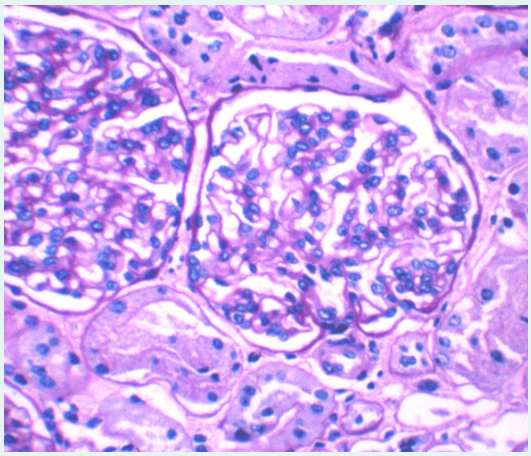

Figure 1: Renal biopsy of patient 1 showing Minimal Change Disease.

Case 2

Thirty four years old male with a positive family history of ADPKD presented with anasarca. His past history was unremarkable. His blood pressure was 180/100 mmHg, and urinary protein excretion was 8.1 g/24 hr. Serum creatinine was 1.6 mg/dl. His albumin concentration was 2 mg/dl and his cholesterol was 350 mg/dl. Connective tissue screen and virology were negative. Abdominal ultrasound and Native CT-scan showed multiple liver and renal cysts.

The patient has been admitted and intrave-

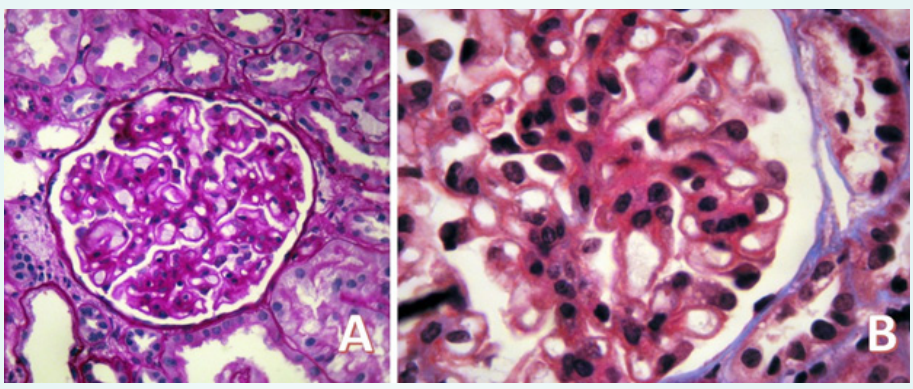

Figure 2 (A and B): Renal biopsy of patient 2 showing Membranous Glomerulonephritis with glomerular basement membrane thickening and spikes.

nous methylprednisolone 500 mg/day for three days initiated. Diltiazem 120 mg twice /day used to control blood pressure and IV furosemide to control volume overload. The patient started to improve and at ten days his oedema started to subside and his serum creatinine was 1.38 mg/dl. Ultra sound guided biopsy from the lower pole of right kidney performed and pathology report disclosed membranous glomerulonephritis (MGN). **Figure 2 (A &B)**

We optimized his antiproteinuric measures with both Ramipril 2.5 mg/dl and diltiazem plus statin. He continued on oral steroids too. After 8 weeks, he was still having oedema and urinary protein excretion of > 4 gm/24 hr. In the view of such response, tacrolimus in a dose of 0.05 mg/kg/ day prescribed. A target trough level of 3-5 ng/ml achieved. At one year after treatment now, his urinary protein is 0.5 gm/24 hr and a stable serum creatinine of 1.1 mg/dl.

Literature review

PubMed search using the combination of (ADPKD AND Nephrotic syndrome) key words yielded 17 titles. The oldest one was in 1990.[6] Actually, the first report was dated back to 1957 when Dalgaard OZ described three instances of nephrotic range proteinuria (>5 g/day) in a report of 122 cases with ADPKD; but renal biopsy data are not available in these series. In 1972, Kida et al reported the first case of ADPKD with nephrotic syndrome due to biopsy-proven minimal change nephrotic syndrome.[7,8]

Since 1972 and through the review by Visciano et al in 2012 to this time there have been only 38 cases (including this report) of ADPKD associated with nephrotic syndrome in which renal lesion documented by histopathological studies. Two of them didn't provide methodological data but renal histopathology diagnosis. 2 In one report, renal biopsy was not performed because of a complete response to steroid therapy in a 9 years old boy.[9]

Table 1: Summary of the literature review

Parameter	Details
Gender	13/36 Female
	23/36 Male
Age	5/36 < 18 years
	31/36 > 18 years
Biopsy	20/36 Open Biopsy
	12/36 Percutaneous Biopsy *
	2/36 CT- Guided biopsy
	1/36 Gingival- Rectal biopsy
	1/36 No biopsy [9]
Renal Histopathology	6/38 Focal segmental glomerulosclerosis (FSGS) [6,10,11-14]
	6/38 Minimal change disease (MCD)* [8,15-18]
	7/38 Membranous Glomerulonephritis (MGN)* [19,20-24]
	3/38 Amyloidosis [25-27]
	3/38 Mesangial proliferative Glomerulonephritis (MES-PGN) [2,28,29]
	2/38 IgA Nephropathy [30,31]
	2/38 Crescentic Glomerulonephritis [32,33]
	2/38 MPO- ANCA Associated vasculitis lesion [34]
	2/38 Lupus Nephritis [5,35]
	1/38 Membranoproliferative Glomerulonephritis [36]
	1/38 Post-infectious Glomerulonephritis [36]
	1/38 Diffuse proliferative Glomerulonephritis (D-PGN) [37]
	1/38 Diabetic glomerulosclerosis [38]
	1/38 Steroid sensitive Nephrotic syndrome (No biopsy) [9]

† For age, gender, and biopsy technique only 36/38 reports were available
* This report

Discussion

Mild to moderate persistent proteinuria (150–1500 mg/day) may be found in a significant number of patients in the middle to late stages of ADPKD. It is an indicator of a more progressive disease. The frequency of occurrence of non-nephrotic proteinuria in ADPKD ranged from 14% to 34% in non-uremic adults to about 80% in adults with advanced ESRD.[4] Nephrotic syndrome is characterized by urine protein excretion greater than 3.5 grams per 1.73 m^2 per day, low serum albumin level, high serum cholesterol level, and peripheral oedema.[33]

ADPKD may affect all segments of the nephron, including the proximal tubule; but it has not been addressed whether alterations of this nephron segment contribute to proteinuria and albuminuria.[39] Thus, nephrotic-range proteinuria observed in some patients with ADPKD could be the consequence of other superimposed glomerular diseases. Since there is no apparent pathogenic link between ADPKD and the different causes of nephrotic syndrome that have been reported in ADPKD

patients, it suggests that they are likely coincidental diseases.

The renal lesion may indicate the pathophysiology. Focal segmental glomerulosclerosis FSGS may be related to the alteration in glomerular haemodynamic in ADPKD and FSGS here may play a role in the progression to end-stage renal disease in a subgroup of ADPKD patients. Moreover, the coincidence of ADPKD and FSGS can be caused by two independent concurrent genetic mutations which are not necessarily related or one single mutation.[2]

Polycystic kidneys have increased susceptibility to infections; incidence of infection has been reported as 21% to 69%. Secondary Amyloidosis (AA) can be seen in course of the disease due to recurrent cyst infections that stimulating chronic inflammatory response.[27]

Renal biopsy and histopathology is the standard approach for diagnosing most of glomerular diseases. The critical issue here is that renal biopsy is an invasive procedure. Most of clinicians avoid percutaneous renal biopsy because of large cysts presumed risk of complications and difficulties in obtaining suitable tissue for diagnosis 2. The reviewed literature indicated that 12/36 (33.3%) of the performed biopsies were percutaneous biopsies performed under ultrasound guidance. In this report, we performed percutaneous biopsy under real time ultrasound guidance from the left and right lower poles of patient 1 and 2 kidneys respectively. These lower poles still had a good representation of the renal parenchyma.

The reluctance of nephrologists to perform an open renal biopsy in ADPKD patients and the real risk and complexity of percutaneous renal biopsy in these patients may affect the real documentation and the correct frequency of such cases.[2]

Other alternatives include CT-guided percutaneous biopsy, laparoscopic, transurethral, or transvenous renal biopsy. In children, a new approach of laparoscopic-percutaneous kidney biopsy may prove beneficial.[40-42]

In this report we had a case of membranous glomerulonephritis. It is essential to know that at the time of diagnosis, the test for Anti PLA2R antibodies for the diagnosis of Membranous Glomerulonephritis (MGN) was not available.

There are no established guidelines for therapeutic management of nephrotic syndrome in ADPKD. Blockade of the renin angiotensin aldosterone system (RAAS) pathway is the main stay of managing hypertension in ADPKD patients. Cyst expansion causes ischemia and the intrarenal renin–angiotensin system would be activated. In addition, RAAS blockade is the main antiproteinuric agents in nephrotic syndrome. Steroid therapy is the first option immune modulatory agent in most of glomerular disease. However, a more aggressive immunosuppressive agent may be used if a proliferative lesion identified on biopsy or as the course of the disease mandates. In this report, normal renal function and < I gm proteinuria maintained over one year with such therapeutic strategy. In reported cases, the responses of patients were dependent on extent of proteinuria, degree of kidney dysfunction and whether renal replacement therapy was needed. [33,43,44]

A better understanding of the pathophysiology and the availability of animal models have facilitated the development of promising candidate drugs to reduce the total kidney volume and to maintain renal function. These include but not limited to the recently added vasopressin antagonists. It is difficult to assess the potential benefit of such therapies leading to a decrease in proteinuria or in the progression of ADPKD toward end-stage renal disease.[45,46]

Conclusion

Nephrotic syndrome occurs in minority of ADPKD patients. Whenever possible renal biopsy still required for the diagnosis. Treatment includes RAAS blockade, steroids and immune therapy according to histopathology and disease progression. Close monitoring of renal function and urinary protein excretion needed to check for progression of kidney disease.

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Abbreviation list: Amyloidosis (**AA**), Autosomal dominant polycystic kidney disease (**ADPKD**), Centimetre (**cm**), Decilitre (**dl**), End stage renal disease (**ESRD**), Focal segmental glomerulosclerosis (**FSGS**), Gram (**g**), Hour (**hr**), Intravenous (**IV**), Kilogram (**Kg**), Milligram (**mg**), millimetre mercury (**mmHg**), minimal change disease (**MCD**), Polycystic disease type 1 (**PKD1**), Polycystic disease type 2 (**PKD2**), Red Blood Cells (**RBCs**), Renin angiotensin aldosterone system (**RAAS**).

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