

Chapter 20

Rapidly Progressive Glomerulonephritis in Autosomal Dominant Polycystic Kidney Disease

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Doi: <http://dx.doi.org/10.15586/codon.pkd.2015.ch20>

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Abstract

Patients with autosomal dominant polycystic kidney disease (ADPKD) can suffer from the same causes of acute kidney injury as the general population. Affected individuals may present with hematuria and proteinuria (usually less than 1g/day). However, nephrotic syndrome and proliferative glomerulonephritis are uncommon in patients with polycystic kidney disease. Development of nephrotic syndrome and / or rapid deterioration in kidney function suggest the presence of another, more aggressive disorder, requiring

In: *Polycystic Kidney Disease*. Xiaogang Li (Editor)
ISBN: 978-0-9944381-0-2; Doi: <http://dx.doi.org/10.15586/codon.pkd.2015>
Codon Publications, Brisbane, Australia

prompt diagnosis and appropriate interventions to mitigate further injury and progression to end stage kidney disease. In this chapter, we will discuss rapidly progressive glomerulonephritis in association with ADPKD.

Key Words: Acute Kidney Injury; Polycystic Kidney Disease; Rapidly Progressive Glomerulonephritis

Introduction

Polycystic kidney disease is the most common cause of monogenic inherited kidney disease and is associated with extra-renal manifestation of cystogenesis primarily in liver and pancreas. It is also associated with saccular aneurysm in the central nervous system (CNS) vasculature, and mitral valve disease (1). Amongst all cystic kidney disorders, autosomal-dominant polycystic kidney disease (ADPKD) is the most frequently diagnosed, affects more than 12 million people worldwide and accounts for about 7-10% of all patients with end stage kidney disease (ESKD) (2). In the majority of cases, the genetic basis for ADPKD has been identified as mutations in one of two large proteins, polycystin 1 and 2 coded by genes *PKD1* and *PKD2* located on chromosome 16 and chromosome 4, respectively (for review, please refer to references (3;4)). There is currently no evidence to support the possibility of mutations in other gene(s) accounting for ADPKD. Ultrasonographic evaluation remains the primary tool for diagnosis because it is inexpensive and widely available. The age-dependent criteria for diagnosis or exclusion of ADPKD have been recently reviewed (5). For patients less than 40 years of age, ultrasonographic criteria may be insufficient to exclude ADPKD. In these circumstances, magnetic resonance imaging (MRI) has proven valuable. A finding of fewer than five kidney cysts by MRI is sufficient to exclude ADPKD (6). Hence, in most cases, genetic testing is not routinely performed for diagnosis of ADPKD.

The phenotypic manifestation of those with mutations in *PKD2* is milder than that seen in individuals with *PKD1* mutations; the former presents with fewer kidney cysts, later onset of hypertension, chronic kidney disease (CKD) and ESKD and the overall survival is better (7). The penetrance of both mutations is highly variable in that cysts and chronic kidney disease may develop at different ages within the same family with identical mutation. The reasons for this are unclear and various hypotheses have been advanced to address this observation (8-10). The 'two-hit' model of cystogenesis has been most widely utilized to explain cystogenesis in ADPKD. The model contends that a germ-line mutation combines with somatic mutations in epithelial cells to promote cyst formation; in this model somatic mutation would be the rate limiting step for cystogenesis (8). A 'three-hit' model of

cystogenesis, in which kidney injury is the third hit, has also been proposed (10). Both of these models are not universally accepted as explanation for variability in cystogenesis and alternative models are being evaluated.

Progressive development of kidney cysts and associated increase in kidney volume are features of ADPKD. Other manifestations of kidney disease include sub-nephrotic range proteinuria, infected cysts associated with constitutional symptoms, and microscopic or macroscopic hematuria (with or without flank pain). Nephrotic range proteinuria (protein excretion > 3.5g/day) is an uncommon occurrence. Whereas development and progression of CKD occurs earlier in individuals with *PKD1* mutation, kidney function may be normal for decades and is not considered a very reliable marker of disease burden. Total kidney volume (TKV) in relation to age provides an accurate estimate of cyst burden and has been associated with hypertension, hematuria and progression of CKD (11;12). Acute renal failure secondary to rapidly progressive glomerular nephritis is rare in those with polycystic kidney disease. In the following sections, we will review the topic of acute renal failure in association with ADPKD. We will start by reviewing a case of rapidly-progressive glomerulonephritis (RPGN) in a patient with ADPKD.

Case

A 43-year-old man, without significant medical or surgical history, presented to the emergency department complaining of bilateral lower extremity edema for two weeks. The patient denied any pertinent family medical history. Physical exam was notable for pitting edema in his lower extremities. Laboratory investigations revealed hematuria, nephrotic range proteinuria (25g/24 hours) and kidney dysfunction (serum creatinine 2.6 mg/dL). Abdominal ultrasound was notable for bilaterally enlarged kidneys with multiple cysts; these findings were confirmed by computed tomographic (CT) scanning. Based on ultrasonographic criteria (age 40-59 years with two or more cysts in each kidney) (5), the patient was diagnosed with ADPKD. A complete serologic evaluation, including hepatitis screen, serology for HIV, hepatitis B and C, syphilis screen, c-anti-neutrophil cytoplasmic antibody (c-ANCA), p-ANCA, anti-GBM anti-nuclear antibodies (ANA) and anti-dsDNA, was performed and was unrevealing. Complements (C3 and C4) levels were within normal limits. Serum and urine protein electrophoresis did not reveal any monoclonal proteins. Initially, empirical treatment with intravenous steroid (methyl prednisolone, 1g daily x 3 days) was administered, then therapy was switched to oral steroid (prednisone, 1 milligram per kilogram daily). Notwithstanding ongoing therapy with prednisone (1mg/kg), renal function declined. Given development oliguria, progressive uremic symptoms and anasarca that was unresponsive to diuretic therapy, intermittent

hemodialysis was initiated. A CT-guided kidney biopsy revealed immune complex glomerulonephritis (positive IgG and C3 on immunofluorescence) with crescent formation and features of membranous nephropathy and (13). Therapy with prednisone was continued and, in addition, treatment with mycophenolate mofetil (500mg, twice daily; escalated to 1500mg twice daily over 2 weeks) was initiated. In order to augment the management of blood pressure and proteinuria, the patient was also treated with Lisinopril (40 mg daily) to manage blood pressure and proteinuria. Over a five-month period, the patient manifested improved kidney function, decreased proteinuria (from 25g to 3g daily), improvement in serum albumin normal levels and increased urine output. Given persistent nephrotic-range proteinuria, oral cyclosporine (75mg twice daily) was added to his treatment regimen. Over the ensuing 3 months, the patient manifested further improvement in physiologic parameters. Accordingly, prednisone dosage was reduced (10mg orally per day). Mycophenylate mofetil (1500 mg twice) and cyclosporine (75 mg twice daily) were maintained. Hemodialysis was subsequently discontinued and he has been off dialysis with stable CKD stage 3 (creatinine clearance 35-40mls/min by 24-hour urine studies) for greater than 2 years. He continues to be monitored closely in the outpatient setting for any changes in renal function. Immunosuppressive agents have been tapered.

Nephrotic syndrome in ADPKD

Nephrotic syndrome is characterized by urine protein excretion greater than 3.5 grams per 1.73 m² per day, low serum albumin level, high serum cholesterol level, and peripheral edema (14). Nephrotic syndrome in adults with polycystic kidney disease was initially reported about fifty-eight years ago (15). In that report, the frequency of nephrotic range proteinuria was 2.5% (3 patients amongst 122 cases). While early reports did not document biopsy evidence of kidney lesions, in general, nephrotic range proteinuria is an uncommon occurrence in persons with ADPKD. Indeed, over the subsequent forty years since the initial report of Dalgaard (15), about thirty-five cases of nephrotic syndrome with documented kidney pathology have been reported (16-18). When nephrotic syndrome has been reported in patients with polycystic kidney disease, the presentation (including nephrotic range proteinuria, edema, hyperlipidemia with and without hypertension), is similar to that seen in patients without polycystic kidney disease. Various etiologies have been identified for nephrotic syndrome in ADPKD patients including membranous glomerulonephritis (MGN), focal and segmental glomerulosclerosis (FSGS), minimal change disease (16;19;20) and immunoglobulin A (IgA) nephropathy (17;21). Of these, FSGS appears to be the most frequently reported cause of nephrotic range proteinuria in adults with ADPKD (16;18;22).

There are no established guidelines for therapeutic management of nephrotic syndrome in ADPKD. Accordingly, as with other cases of nephrotic syndrome, the mainstay of therapy involves angiotensin converting enzyme inhibitors or angiotensin II receptor blockers and corticosteroid therapy. However, a more aggressive immunosuppressive agent may be needed if proliferative lesions (for example, mesangioproliferative glomerulonephritis) are identified on kidney biopsy specimen. In reported cases, the responses of patients were dependent on extent of proteinuria, degree of kidney dysfunction and whether renal replacement therapy was needed (16;18;22).

Rapidly progressive glomerulonephritis

RPGN, also termed crescentic GN, is a pathologic entity primarily characterized by extra-capillary cellular proliferation in Bowman's space. Crescents, involving greater than fifty percent of glomeruli, are derived from epithelial cells and activated macrophages. Included in this group of diseases are small vessel vasculitis, Goodpasture's syndrome and ANCA associated vasculitis (23). In children and adolescents, Henoch-Schönlein purpura is more common while in women of childbearing age, systemic lupus nephritis is a more frequent cause of RPGN (24).

Three categories of RPGN have been described: type 1, presence of immune deposits in basement membrane; type 2, immune deposits in the mesangium and basement membrane; type 3, absence of glomerular immune deposit (23;25;26). Type 3 RPGN is the most common and accounts for about 50-60% of RPGN, Type 2 accounts for 15-20 %, and Type 1 is the least common (about 10% of RPGN). Type 1 RPGN primarily includes Goodpasture's syndrome (anti-glomerular basement membrane glomerulonephritis, anti-GBM GN) whereas Type 2 RPGN encompasses a diverse group of conditions including systemic lupus nephritis, IgA nephritis, Henoch-Schönlein purpura and immune complex mediated membranoproliferative glomerulonephritis. Type 3 RPGN includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (27).

Clinically, all patients with RPGN present with nephrotic syndrome and rapid decline in kidney function. In addition, extra-renal signs and symptoms (arthralgias, skin rash, pericarditis, peripheral neuropathy, rhinitis, sinusitis) may be present. Patients affected by RPGN are at high risk for progression to ESKD. Early diagnosis and therapeutic intervention is indicated to mitigate progression to ESKD. Renal biopsy is important for diagnosis, prognosis and to guide therapy.

Treatment is based on the combination of corticosteroids and cytotoxic agents (cyclophosphamide). In addition, plasma exchange (PLEX) is indicated in patients with Goodpasture's syndrome (28;29) and may be beneficial in resistant cases of type 2 RPGN. PLEX is indicated in patients with alveolar hemorrhage (30;31). Likewise, for patients with ANCA-associated vasculitis and RPGN, PLEX augments therapy with corticosteroids and cytotoxic agents and positively impacts patients' outcome and survival (32;33). Rituximab plus corticosteroids are as effective as cyclophosphamide for treatment of patients with type 3 RPGN (34;35). However, the effectiveness of Rituximab plus corticosteroid regimen as rescue therapy in resistant type RPGN disorders like lupus crescentic nephritis is unclear (36).

Proliferative glomerulonephritis in ADPKD

Crescentic glomerulonephritis is a rare occurrence in patients those with ADPKD. In addition to the case highlighted above (13), three additional cases have been reported (37;38); ADPKD diagnosis was based on ultrasonographic criteria in these cases. All cases were characterized by nephrotic range proteinuria, hematuria and acute kidney injury indicated by the rapid decline in kidney function. In the most recently reported cases (38), both patients had ANCA-associated crescentic glomerulonephritis without evidence of vasculitis. In the case we presented in this review, the cause of acute kidney injury and nephrotic syndrome was attributed to crescentic glomerulonephritis rather than the patient's underlying polycystic kidney disease.

The reasons for occurrence of glomerulonephropathies, with massive proteinuria, in ADPKD remain unclear. The three patients in the other reports (37;38) were older than our patient and one of the two patients developed ESKD and remained dialysis-dependent. However, common features or specific risk factors for development of RPGN amongst the four cases were unknown. In the current case, common causes of rapidly progressive kidney failure and nephrotic range proteinuria, including post-infectious causes, hepatitis B and C and IgA nephropathy were excluded. Given the limited number of cases of RPGN in patients with ADPKD, ascertaining mechanism(s) will be challenging.

All reported series emphasize the importance of performing kidney biopsies in patients with ADPKD who develop nephrotic range proteinuria. In addition to identifying the cause of proteinuria and acute kidney injury in these patients, renal biopsy informs appropriate management of proteinuria. In our patient, the biopsy findings of crescentic GN mandated a more aggressive, immunosuppressive regimen in management of the patient.

Table 1. Details on patients with PKD and crescentic glomerulonephritis

Authors	Age (years)	Gender	Acute Kidney Injury	Nephrotic Range Proteinuria (g/day)	Hematuria (microscopic)	Renal Histopathology	Treatment	Outcome
Licina et. al. (37)	69	F	Yes	NQ / NR	Yes	CresGN	CS	Cr 2.4 mg/dL
Sumida et. al. (38)	60	F	Yes	Yes (4.5)	Yes	ANCA-MPO CresGN	CS	Cr 2.8 mg/dL Proteinuria (0.2g/day)
Sumida et. al. (38) CresGN	54	F	Yes	Yes (5.7)	Yes	ANCA-MPO CresGN	CS, PLEX	HD-dependent
Maggard et. al. (13)	45	M	Yes	Yes (25)	Yes	ICGN / MGN Cres-GN	CS, MMF CsA, ACEi	HD x 8 months Cr 2.6 Proteinuria (0.8 g/day)

ACEi: angiotensin converting enzyme inhibitor; ANCA: anti-neutrophil cytoplasmic antibody; NQ: Not quantified; NR: Not reported; CS: Corticosteroid; CsA – Cyclosporin; CresGN: Crescentic Glomerulonephritis; HD: Hemodialysis; ICGN: Immune complex glomerulonephritis; MPO: Myeloperoxidase; MMF: Mycophenolate Mofetil; PLEX Plasma Exchange.

Given the rarity of RPGN (or crescentic GN) in patients with polycystic kidney disease, there are no established guidelines on management. ADPKD in this patient was diagnosed on presentation and in view of the superimposed RPGN, management of the latter was the primary goal. The combination of steroid and mycophenolate mofetil was chosen over steroids and cyclophosphamide because of better side effect profile of mycophenolate mofetil. Cyclosporine was added to enhance management of proteinuria. The patient responded well to the combination of steroids, mycophenolate mofetil and cyclosporine. In the other reported cases of crescentic GN in patients with ADPKD, treatment included corticosteroids alone or in combination with PLEX (37;38). Like our patient, in two of the three reported cases, kidney function improved but did not return to normal (serum creatinine range 2.4 - 2.8 mg/dL); the third patient (one of two with ANCA-associated glomerulonephritis, without vasculitis) remains dialysis-dependent (Table 1).

Conclusions

Proteinuria (<1g/day) is not uncommon in individuals with polycystic kidney disease but nephrotic range protein excretion (>3.5g/day) is an infrequent occurrence. Intermittent hematuria in adults with polycystic kidney disease, without significant changes in urine protein loss may reflect cyst hemorrhage. This is more likely if hematuria is accompanied by flank pain without other constitutional symptoms (like fever) that would suggest an infectious process. The development of nephrotic range proteinuria in association with a rapid decline in kidney function should prompt consideration of glomerulonephritis. We illustrate the importance of prompt diagnosis of nephritic syndrome in patients with polycystic kidney disease especially when there is acute deterioration of kidney function; we also emphasize the importance of kidney biopsy to define histopathologic lesion(s). In addition to furnishing information that cannot be obtained from conventional imaging and serologic analyses, kidney biopsy provides prognostic information and serves to guide therapy.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

Acknowledgement

Faculty members, Division of Nephrology and Hypertension, Department of Medicine, University of Florida, Jacksonville. We thank the Division of Nephrology and

Hypertension, Department of Medicine, University of Florida (Jacksonville) for support of this undertaking.

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