CLINICAL VIGNETTE

A Young Man with Polycystic Kidneys' Journey to End Stage Kidney Failure

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A 39-year-old man was diagnosed with hypertension at age 21, with baseline creatinine of 1.0. Ten years later, his mother was incidentally diagnosed with enlarged cystic kidneys on a liver ultrasound, and the patient was referred to nephrology. Ultrasound confirmed large kidneys with numerous cysts. He was treated with losartan and amlodipine to manage blood pressure (BP) and Polycystic Kidney Disease (PKD), along with lifestyle modifications including increased water intake, low salt meals and decreased caffeine.

Two years later, at age 33, he was started on Vasopressin receptor antagonist (Tolvaptan), the first FDA approved medication for PKD, along with close monitoring of his kidneys' sizes, volume and GFR. He remained on treatment for 5 years. His BMI was normal at 22 kg/m2 and he was active.

At age 38, the patient had a bike accident and was admitted to the hospital with severe flank pain and gross hematuria. He was found with decreased hemoglobin to 6.7 from baseline of 10-11 due to bleeding. Non-contrast CT confirmed ruptured cysts and patient received supportive care including IV fluids and blood products along with close monitoring for need of dialysis in the setting of acute kidney injury (AKI) on chronic kidney disease (CKD). His creatinine increased from 3.1 to 6.7 with GFR decline from 24 to 10 mL/min/1.73. Six months after cyst rupture his disease progressed to End stage kidney disease (ESKD).

Table 1 summarizes laboratory and diagnostic findings from the onset of hypertension at age 21 till ESKD at age 38.

Table 1.

Year	2007 2008	2009 2010	2011 2012	2013 2014	2015 2016	2017 2018	2019 2020	2021 2022	2023
Creatinine	1.1	1.1	1.0	1.2-1.3	1.4-1.5	1.6-1.8	1.8-2.1	**2.3-3.1**	**4.9-6.7-9**
GFR per CKD Epi equation mL/min/1.73 square meters	>80	>80	>80	87>72	69>67	60>53	53>47	**34>24**	**14>10>7**
Other tests	BMI 22 Kg/m2		U/A: Negative blood and protein	U/A: 1-2 +protein	Ultra Sound: enlarged kidneys consistent with PKD Right Kidney 16.8 cm/numerable kidney cysts Left Kidney 17 cm and Total Kidney Volumes >1200ml	Nuclear Med: GFR 66.4 ml/min/1.73 Urine Alb/Cr: 126	U/A: Negative blood Urine Alb/Cr: 229	Ultra sound: Right kidney Length = 22.0 cm Left kidney Length = 16.8 cm.	

Discussion

ADPKD, which is the leading genetic cause of renal failure, is characterized by fluid-filled cyst formation in the kidney and relentless growth and formation of cyst that can lead to parenchymal destruction and renal failure. The estimated worldwide prevalence is 12.5 million and is the cause of ESRD in 10% of patients across all ethnic groups.[1] Kidneys are impacted with

hypertension, albuminuria, hematuria, cyst rupture, cysts hemorrhage, infection, and urine concentration defects.[2]

Hypertension is common, and associated with increased total kidney volume (TKV), activation of the renin–angiotensin–aldosterone system, and progression of kidney disease.[3] Hypertension is strongly associated with cardiovascular morbidity and mortality and risk for ESKD in ADPKD. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are the first-line treatment for hypertension in ADPKD patients and the HALT-PKD clinical trials confirmed treatment benefit. Intensive BP control (95-110/60-75 mm Hg) was associated with 14.2% lower increase in total kidney volume and 3.77% lower urinary albumin excretion.[3,4] The percentage change in the total kidney volume over time and baseline height adjusted TKV (htTKV) ≥600 cc/m predicted the risk of developing renal insufficiency in ADPKD patients at high risk for renal disease progression within 8 years of follow-up, qualifying htTKV as a prognostic biomarker in ADPKD.[3,4]

Cyst hemorrhage typically presents with flank pain or gross hematuria, which generally resolves within a week with conservative therapy. In rare cases, cyst rupture can result in life-threatening retroperitoneal hemorrhage, requiring immediate medical attention.[4]

New targets for lifestyle and medical interventions in ADPKD have been proposed based on improved mechanistic knowledge.

Figure 1 summarizes recommended lifestyle modifications.

Figure 1: Lifestyle modifications to decrease the rate of progression of PKD.

Dietary salt restriction to 2.3 to 3 g/d is advised as high salt intake stimulates vasopressin secretion, increased plasma levels of endogenous cardiotonic steroids, and increases kidney production of TGF-β.[5] Blood pressure control (<110/75 mm Hg) can delay increase in TKV. The antidiuretic hormone arginine vasopressin (AVP) is thought to have a detrimental role in ADPKD and increased water consumption, can decrease vasopressin levels sufficient to reach urine osmolarity < 280 mOsm/kg, about 2-3 liter/day urine volume, which indicates suppression of vasopressin secretion.[5]

Caffeine-like substances may promote and accelerate cyst growth in PKD via increase in cAMP. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort reported caffeine was statistically significant when modeling in both unadjusted and adjusted models.[6] Previous studies had not accounted for the wide individual variation in caffeine metabolism, which could effect any associations.[7]

High caffeine intake has potential effects on intracellular cAMP levels, and the patient was advised to decrease the amount of coffee intake. The proliferation of epithelial cells in cyst walls and the rate of fluid secretion into cysts are increased by cyclic AMP (cAMP). Therefore, stimuli that cause increased cAMP production should also be avoided in ADPKD. These include some herbs such as forskolin and the patient was advised not to use any herbal medication and not to use any protein supplements that are used by athletes.[5]

The FDA approved tolvaptan as a treatment option for ADPKD patients in 2018. A randomized, double-blind, placebo-controlled clinical trial by Torres et al in 2017 reported tolvaptan treatment was associated with a slower decline in eGFR compared to placebo (2.34 ml/min/yr vs 3.61 ml/min/yr, $p<0.001$). Our patient started to take tolvaptan in 2018 although it was held after the trauma.[8]

Medical Management

Gross hematuria after trauma is a classic presenting feature of autosomal dominant polycystic kidney disease. This can be seen in contact sports but may also occur without antecedent abdominal trauma. With supportive therapy, gross hematuria usually subsides within days.[9] If severe or persistent, cyst hemorrhage may be associated with a decline in kidney function. Patients should be encouraged to avoid situations that carry a high risk of abdominal trauma (e.g., high-impact sports), and blood pressure should be maintained below 130/80 mm Hg. Bed rest, analgesics, and hydration enough to increase the urinary flow rate to 2 to 3 liters per day are also recommended. The use of anticoagulants, including low-dose aspirin, should be avoided in the absence of a strong indication in patients with gross hematuria. With massive cyst bleeding, patients may present with signs and symptoms of hemorrhagic shock requiring prompt evaluation and management.[10] Treatment often includes close observation in the Intensive Care Unit (ICU), routine monitoring of hemoglobin levels, resuscitation with blood products aiming for hemoglobin of over 7 g/dL and use of vasopressors as necessary following adequate resuscitation to maintain a mean arterial pressure of at least 65 mmHg.[9,10]

A recent study has shown that persistent bleeding in a patient who underwent multiple percutaneous embolization was treated with Tranexamic acid for 9 days. The use of tranexamic acid has been explored to control cyst bleeding in ADPKD patients. It is hypothesized that tranexamic acid works by counteracting local and systemic activation of fibrinolysis by urokinase in ADPKD. In a case series, tranexamic acid was administered to 8 ADPKD patients presenting with gross hematuria unresponsive to conventional treatment. Bleeding was controlled within

2-5 days of treatment and no adverse effects of anti-fibrinolytic therapy were noted. Tranexamic acid may be considered in the appropriate clinical setting when conventional measures fail to mitigate cyst bleeding.[10]

Studies have suggested when conservative therapies fail and/or in the presence of active bleeding demonstrated on angiography, interventional radiology (IR)-guided percutaneous embolization is recommended. In severe cases with refractory bleeding or failure of embolization, urgent nephrectomy may be indicated.[10]

Renal transplantation is considered the optimal choice for renal replacement therapy (RRT) in individuals with ADPKD. Living kidney donation, particularly preemptive donation, is associated with better outcomes. However, due to the limited number of potential donors within affected families, individual and family counseling may be necessary to determine donation priorities.[11] Renal T2-weighted MRI can be used to identify related living donors for kidney transplantation in ADPKD patients for individuals who are not suitable candidates for transplantation or are waiting for a suitable donor, hemodialysis (HD) or peritoneal dialysis (PD) are suitable alternatives. While ADPKD may pose some challenges for individuals undergoing PD, such as the increased risk for abdominal wall hernias, intra-abdominal space restrictions, and a higher prevalence of colonic diverticula, it is not considered a contraindication for PD. The choice of RRT should be made based on individual patient characteristics, preferences, and medical factors.[12]

It is not recommended to routinely remove kidneys before transplantation in individuals with ADPKD due to the significant morbidity and mortality associated with the procedure. Nephrectomy may be considered for individuals who have recurrent and/or severe infection, symptomatic nephrolithiasis, recurrent and/or severe bleeding, intractable pain, suspicion of renal cancer, or space restrictions prior to transplantation. It should be noted that the size of the kidney typically decreases after transplantation. Therefore, the decision to undergo nephrectomy prior to transplantation should be made on a case-by-case basis.[11]

After transplantation, the morbidity risk in ADPKD patients appears to be similar to other non-diabetic transplant recipients. However, some specific complications have been reported to be more frequent in ADPKD patients, including new-onset diabetes, gastrointestinal complications, erythrocytosis, urinary tract infections, thromboembolic complications, and hemorrhagic stroke.[12]

It is important for healthcare providers to monitor and actively manage potential complications in PKD patients who have undergone transplantation. Regular follow-up, medication management, and lifestyle modifications may prevent or minimize these complications.

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