Case Report

Adult Polycystic Kidney Disease: A Disorder of Connective Tissue?

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Abstract: Adult polycystic kidney disease (APCKD) is one of the most common serious inherited disorders. Many affected patients succumb to the renal and non-renal manifestations of this autosomal dominant disease. The disease is characterized by cyst formation in several organs, most obvious of which is in the renal parenchyma. Other features associated with the disease include hepatic fibrosis, hepatic, pancreatic and splenic cyst formation, Berry aneurysms, colonic diverticulae, hernias and cardiac valvular disorders. Rupture of Berry aneurysm is a sudden and often fatal manifestation in some unsuspected cases of APCKD. We recently examined one surgically removed kidney from a 15-year-old male patient with APCKD. In addition to the classical cystic change, extensive changes in renal parenchymal matrix and vasculature are also present. The excessive and weak matrix may contribute to dilatations of both renal tubules giving rise to cysts and the blood vessels. Our findings suggest that APCKD may be a connective tissue disorder in which alteration of extracellular matrix may be a common denominator for the manifestations and organ pleotropism of APCKD.

Key Words: Adult polycystic kidney disease, renal cyst, hepatic cyst, hepatic fibrosis, Berry aneurysm, hernia, diverticula, cardiac valvular disorders

Introduction

Adult Polycystic Kidney Disease (APCKD) is one of the most common autosomal dominant inherited disorders. In addition to the obvious and prominent renal cysts, the disease is often associated with other anomalies including cysts in various organs such as liver, spleen and pancreas, Berry aneurysm and hernias of various types. Although renal cysts had been the center of attraction, very little if any attention had been paid to the changes in the vasculature and extracellular matrix of renal parenchyma. We recently examined one polycystic kidney and found significant renal vascular changes, suggesting a possible role of abnormal fibrous matrix of the renal parenchyma in the pathogenesis of the protean disease with apparently divergent manifestations.

Clinical History and Pathological Findings

A 15-year-old male presented with excruciating and unbearable unilateral flank pain. Imaging studies confirmed bilateral polycystic renal disease. The kidney on the pain side was almost totally replaced by cysts while the contralateral kidney had slightly better preserved renal function. On insistence of the patient and his parents, and due to unbearable pain and the fact that this kidney had little function left, a unilateral nephrectomy was performed and the kidney was submitted for histopathological evaluation. Grossly, the kidney measured 17 X 8 x 6.5 cm with numerous cysts of variable size and scant intervening renal parenchyma. Histologically, the cysts were lined by low cuboidal to flat epithelial cells (**Figure 1A**). There was no evidence of epithelial hyperplasia. The renal parenchyma contained variably sized blood vessels. Many of these were focally compressed, dilated, and tortuous (**Figures 1B** and **C**). Some of these had led to focal frank hemorrhages (**Figure 1D**). The collagenous tissue was edematous and excessive causing compression of both tubules and the blood vessels (**Figure 2A** and **B**). A diagnosis of adult polycystic kidney
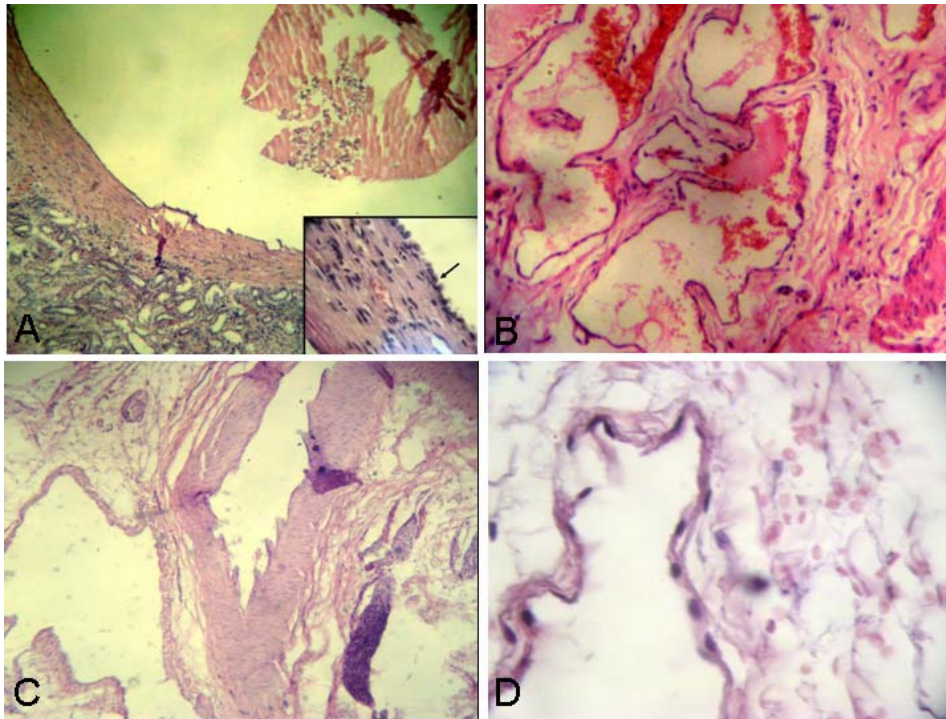
Figure 1 A. Cyst lined by low cuboidal to flat epithelial cells (H&E x 40). Inset showing high power image of the cystic wall lined by cuboidal epithelium (H&E x 400). **B.** Aneurysmal, thin dilated vessels lined by horizontally oriented endothelial cells (H&E x 200). **C.** Thick, dilated vessels with excessive surrounding matrix and edema (H&E x 100). **D.** Extravasation of red blood cells and edema surrounding a vessel lined by horizontally oriented endothelial cells (H&E x 400).
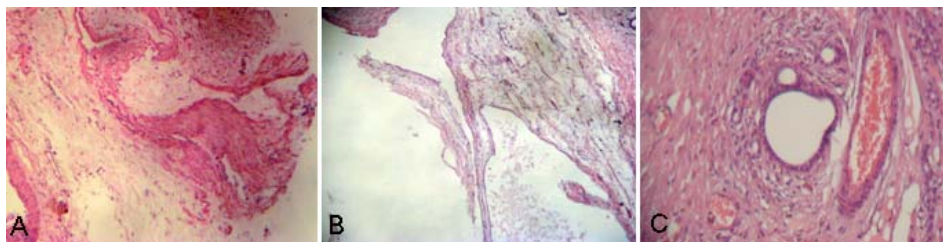

Figure 2 A. Hybrid, dilated vessels surrounded by excessive matrix and edema, compressing the blood vessels (H&E x 100). **B.** Excessive matrix and edema around cystic tubules (H&E x 100). **C.** Liver biopsy in Caroli's syndrome showing dense fibrosis with compression of the bile duct leading to cyst formation. Please note dilations of various types of vessels and extravasations of red blood cells in the stroma (H&E x 100).

disease was confirmed histologically and the physicians were alerted to look for other conditions associated with the disease such as Berry aneurysm and proper followup.

Discussion

Autosomal dominant polycystic kidney disease is one of the most common hereditary disorders. The term "adult polycystic kidney disease" belies its true scope by focusing on the kidney and by confining the disorder to adults. In fact, autosomal dominant polycystic kidney disease is a systemic hereditary disorder that may occur at any time in life, including in utero [1, 2], and is characterized

by cyst formation in ductal organs, particularly kidney and liver, and abnormalities in the gastrointestinal, cardiovascular, and musculoskeletal systems [3].

Apart from the classical cysts, changes in the renal vasculature including compression, dilatation and frequent focal parenchymal hemorrhage and edema are also present. The extracellular collagen matrix is also found to contain extravasated red blood cells and edematous. The latter is probably due to accumulation of plasma associated with hemorrhage. In the present case, hemorrhage may be the cause for the excruciating pain in our patient. The matrix is excessive and edematous leading to compression of both tubules and the blood vessels. It is clear that the "cysts" are actually dilated tubules. Such dilation and cyst formation also occur in other organs in APCKD, such as liver, pancreas and spleen. Cyst formation can occur in other diseases unrelated to APCKD, such as fibrocystic disease of breast. In this situation, fibrosis leads to compression of the breast ducts that in turn results in cystic dilatation of the proximal segments of the ducts. Unlike the cystic change in APCKD, there is an element of epithelial cell hyperplasia in fibrocystic disease of breast. Similar dilations are seen in skin biopsies of patients treated with steroids.

Extrarenal manifestations include liver cysts, pancreatic cysts and splenic cysts in 29-73%, 9% and 5% of APCKD patients, respectively. Cysts have also been reported in thyroid, parathyroid, lung, brain, pituitary gland, pineal gland, ovary, uterus, testis, seminal vesicles, epididymis, bladder, and peritoneum. Aneurysms of cerebral arteries (Berry aneurysms) have been found in 3-50% of patients. A variety of cardiac and aortic abnormalities have been associated with APCKD. These include aortic root dilatation, aortic regurgitation, bicuspid aortic valves, coarctation of the aorta, mitral regurgitation, and abdominal aortic aneurysm [4, 5]. Polycystic disease associated with intracranial arteriovenous malformation is yet another extrarenal manifestation [6]. The association of APCKD with other manifestations of collagen abnormalities supports the notion that APCKD may actually represent a collagen matrix disease. These extrarenal manifestations are not seen in neonates and infants [7, 8, 9, 10, 11, 12], however, suggesting that it takes time to gather more

matrix to compress and/or to weaken the matrix in order to form aneurysms, cysts and hernias.

Although there is no apparent uniformity of defects in the extracellular matrix, immunocytochemical techniques and measurements of messenger RNA levels for matrix constituents identify matrix abnormalities not only in human autosomal dominant disease but also in a variety of experimental models, suggesting a central role for matrix alteration in cystogenesis [13, 14, 15, 16]. Moreover, an abnormal basement membrane has been observed in biopsy specimens from subjects with a family history of polycystic kidney disease before cysts can be detected [17]. Late in the disease the basement membrane surrounding the cysts is an abnormal, thickened mass of interwoven fibrils [18, 19]. In addition, the array of systemic abnormalities in polycystic kidney disease is compatible with a defect in the composition of the extracellular matrix. Aneurysms, diverticulae and various forms of hernia also clearly point to a defect in collagen matrix.

ADPKD is an inherited condition comprising at least 3 phenotypically indistinguishable but genetically distinct entities. The specific form that develops depends on which of 3 genes—polycystic kidney disease or polycystin (PKD) 1, PKD2, or PKD3—becomes mutated. In 90% of patients, the affected gene is located on short arm of chromosome 16(16p); in 10% of patients, the disease arises from a spontaneous mutation. ADPKD is transmitted as an autosomal dominant trait, with almost 100% penetrance if patients live long enough. Many investigators have postulated that defective polycystins appear to contribute to cyst formation by affecting epithelial cell maturation, resulting in the development of cysts of varying sizes in the cortex and medulla [20, 21].

Patients with PKD2, as well as those with PKD1, are at risk of intracranial aneurysm. The position of the mutation in PKD1 is predictive for development of intracranial aneurysms (59 mutations are more commonly associated with vascular disease) and is therefore of prognostic importance. Since the PKD1 phenotype is associated with mutation position, the disease is not simply due to loss of all disease allele products [22].

Reeders [23] put forward an interesting 2-hit mutational hypothesis for PKD1. The hypothesis suggests that at the sites of cyst formation, a somatic mutation occurs in the wild type allele of PKD1 on chromosome 16. A prediction of the 2-hit model is that renal cysts will occasionally be found in persons without an inherited predisposition as a result of two somatic mutations occurring in a single cell. The 2-hit model also predicts that the number of cysts would increase with age in PKD1.

The International Polycystic Kidney Disease Consortium [24] reported the complete structure of the PKD1 gene and its protein. PKD1 protein is involved in adhesive protein-protein and protein-carbohydrate interactions in the extracellular compartment. They proposed a hypothesis that links the predicted properties of the protein with the phenotypic features of autosomal dominant PKD.

Hughes *et al* [25] isolated the full-length PKD1 gene using an exon-linking strategy. They took RNA from a cell line containing PKD1. The predicted PKD1 protein, named polycystin, is a glycoprotein with multiple transmembrane domains and a cytoplasmic C-tail. The N-terminal extracellular region of over 2,500 amino acids contains leucine-rich repeats, a C-type lectin, 16 immunoglobulin-like repeats, and 4 type III fibronectin-related domains. The findings indicated that polycystin is an integral membrane protein involved in cell-cell/matrix interactions.

Ward *et al* [26] suggested that the major role of polycystin is in the maintenance of renal epithelial differentiation and organization from early fetal life. Polycystin expression, monitored at the mRNA level and by immunohistochemistry, appeared higher in cystic epithelia, indicating that the disease does not result from complete loss of the protein.

Qian *et al* [27] developed a novel method for isolating renal cystic epithelia from single cysts and showed that individual renal cysts in PKD1 are monoclonal. Loss of heterozygosity (LOH) was discovered within a subset of cysts for 2 closely linked polymorphic markers located within the PKD1 gene. Genetic analysis revealed that it was the normal haplotype that was lost. The findings provided a molecular explanation for the focal nature of cyst formation and a probable mechanism

whereby mutations cause disease. The high rate at which 'second hits' must occur to account for the large number of cysts observed, suggested that unique structural features of the PKD1 gene may be responsible for its mutability. They postulated that the polypyrimidine tract may cause ongoing errors in its transcription-coupled repair, thus resulting in a high frequency of somatic mutation. Thus, they concluded that PKD1 is a recessive disorder when viewed at the level of the individual renal lesions.

We have summarized these various postulations in **Table 1**. However none of the hypothesis regarding active role of renal tubular epithelium explains the divergent and rather vast pleotropism seen in APCKD. The epithelial cells in the renal tubules are compressed and atrophic rather than hypertrophic. This is for example in sharp contrast to the fibrocystic disease of breast where epithelial hyperplasia may contribute to the active blockage of the ducts leading to cystic dilatations. Berry aneurysms for example have no epithelium. It seems that in addition to the primary genetically determined stromal changes in APCKD, secondary changes due to plasma and/ or blood exudation from ruptured vessels activating fibroblasts may accentuate and heighten the disease process.

We had seen a case of Caroli's syndrome a few years back in our department. Review of the slides revealed dense fibrosis not only compressing the bile ducts and forming cysts of various diameters but also causing vascular dilation and rupture. Extravasated red blood cells were also seen (**Figure 2C**). It is a common observation that prolonged edema and/or exudation of plasma or blood leads to fibrosis that may sustain and perpetuate the disease process both in ADPKD and in liver of Caroli's syndrome. If defective and/or excessive collagen is the central hub, it would not be surprising to see Caroli's syndrome patients having polycystic kidney disease and APCKD patients having hepatic cysts. In many instances, it may be the same disease with more severe expression of one phenotypic feature over others.

In conclusion, we propose that the renal vascular changes further supports the hypothesis that ADPKD may in reality be a collagen matrix disease with marked

Table 1 Various proposed molecular mechanisms in the pathogenesis of APCKD

| Authors	Genetics
Deltas and Koptides M [20, 21]	The specific form of disease that develops depends on which of the 3 genes—*PKD1, PKD2,* or *PKD3*—becomes mutated.
Reeders [23]	2-hit mutational hypothesis for PKD1
The International Polycystic Kidney Disease Consortium [24]	PKD1 protein is involved in adhesive protein-protein and protein-carbohydrate interactions in the extracellular compartment.
Hughes *et al* [25]	The predicted PKD1 protein, called polycystin, is a glycoprotein with multiple transmembrane domains and a cytoplasmic C-tail. The N-terminal extracellular region of over 2,500 amino acids contains leucine-rich repeats, a C-type lectin, 16 immunoglobulin-like repeats, and 4 type III fibronectin-related domains. The findings indicate that polycystin is an integral membrane protein involved in cell-cell/matrix interactions.
Ward *et al* [26]	Polycystin expression, monitored at the mRNA level and by immunohistochemistry, is higher in cystic epithelia, indicating that the disease does not result from complete loss of the protein.
Qian *et al* [27]	Renal cystic epithelia, isolated from single cysts showed that individual renal cysts in PKD1 are monoclonal; Loss of heterozygosity (LOH) was discovered within a subset of cysts for 2 closely linked polymorphic markers located within the PKD1 gene; The polypyrimidine tract may cause ongoing errors in its transcription-coupled repair, thus resulting in a high frequency of somatic mutation.
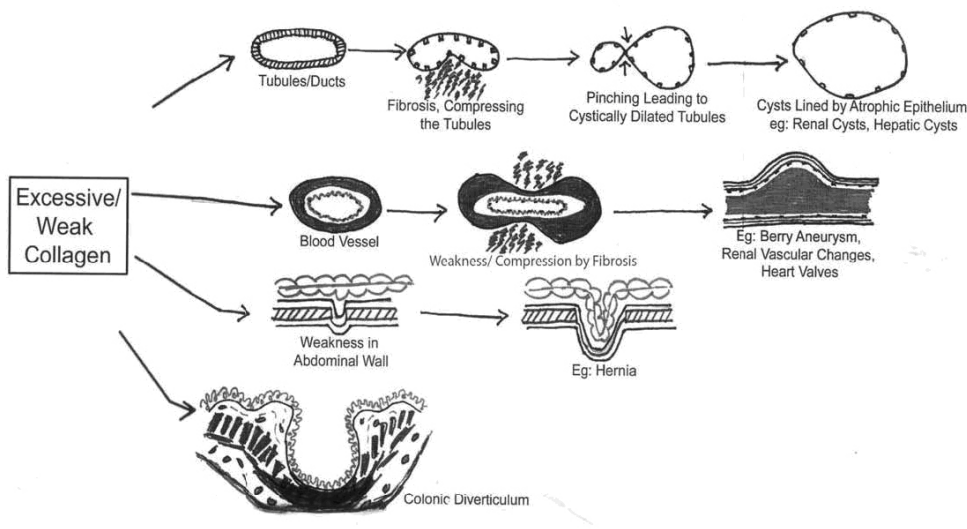
Figure 3 Central role of excessive/weak collagen in the pathogenesis of different manifestations of APCKD

pleotropism and varied expressivity. The vascular changes may play an important role in the pathogenesis, evolution and perpetuation of the disease process due to edema, rupture, hemorrhages and fibrosis which in turn leads to compression and dilatation of tubules as well as blood vessels. The weak and/or excessive collagen appears to be the common pathogenic factor in such apparently varied conditions as Berry aneurysms, hernias, cardiac valvular diseases, diverticulae and cysts in various organs (**Figure 3**). Further genetic and morphological observational studies are required to meticulously delineate the collagen matrix abnormalities associated with various phenotypic expressions in different organs.

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