Update on adult renal cystic diseases

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A wide spectrum of hereditary and non-hereditary disorders results in development of renal cysts in adult patients. Hereditary renal cystic syndromes include autosomal dominant polycystic kidney disease, medullary cystic kidney disease, von Hippel-Lindau syndrome, and tuberous sclerosis. The non-hereditary disorders that predispose to the formation of renal cysts include acquired cystic kidney disease, medullary sponge kidney, multicystic dysplastic kidney, and localized renal cystic disease (Table 1).[1] Recent advances in genetics and molecular biology have shown that functional and structural abnormality of the primary cilia of the renal tubular epithelial cells subsequently lead to hereditary renal cystic diseases. Non-hereditary renal cystic diseases result from abnormal renal embryogenesis and/or neoplastic mechanisms. Many adult renal cystic diseases show characteristic imaging findings that may help in accurate diagnosis. Improved understanding of pathophysiologic mechanisms has led to development and testing of novel drugs for some of these diseases. In addition to diagnosis, imaging studies play a pivotal role in long-term surveillance, assessing prognosis, and testing efficacy of drugs.

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Table 1: Spectrum of renal cystic diseases in adult patients

Hereditary Conditions	Non-hereditary Conditions
Autosomal dominant polycystic kidney disease	Acquired cystic kidney disease
Medullary cystic kidney disease	Medullary sponge kidney
von Hippel-Lindau disease	Multicystic dysplastic kidney
Tuberous sclerosis	Localized cystic kidney disease

Hereditary renal cystic diseases

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited renal cystic disease, is characterized by marked enlargement of bilateral kidneys and multiple expansile cysts.[2,3] ADPKD is a heterogenetic disorder caused by mutations in *PKD1* (located at chromosome 16p13 and encodes for polycystin-1 protein) and *PKD2* genes (located at 4q21 and encodes for polycystin-2 protein). Abnormality of PKD1 gene is seen in 85% of ADPKD patients and that of PKD2 gene results in the remainder.[1,4] The polycystin-1 and polycystin-2 proteins are located within the primary cilia of renal tubular epithelial cells and play a major role in renal tubular homeostasis and epithelial proliferation.[5,6] Disruption of polycystin signaling in ADPKD causes inability of tubular epithelial cells to sense mechanical cues that normally regulate tissue morphogenesis and result in tubular ectasia due to over-

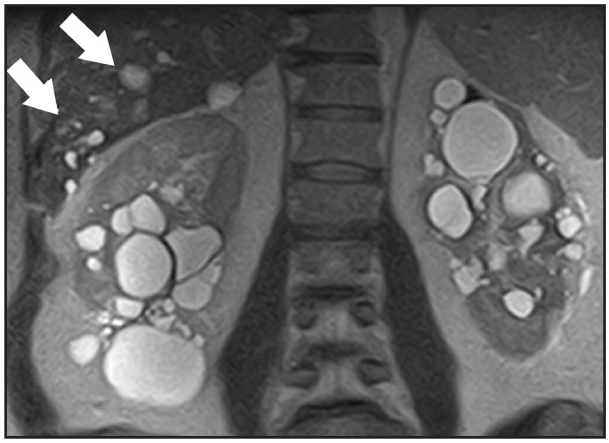

FIGURE 1. *A 45-year-old man with autosomal dominant polycystic kidney disease (ADPKD). Coronal T2-weighted MR image demonstrates bilateral enlarged kidneys with multiple renal cysts and hepatic cysts (arrows) consistent with the diagnosis of ADPKD.*

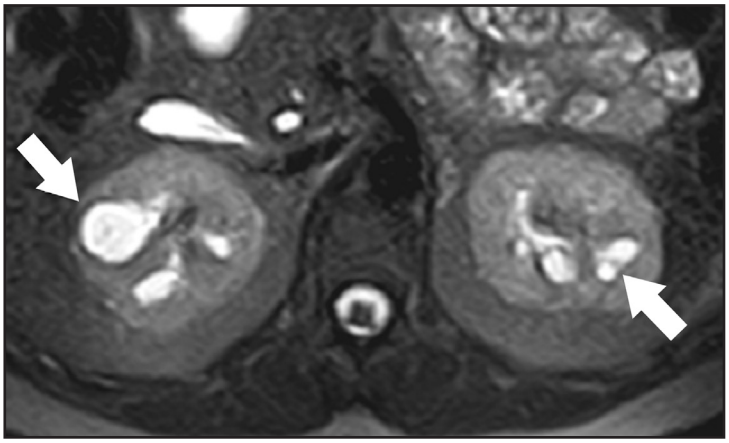

FIGURE 2. *Medullary cystic kidney disease (MCKD) in a 42-year-old woman with suspicious clinical and laboratory findings. Axial T2-weighted MR image demonstrates bilateral normal-sized kidneys with multiple cysts in the medulla (arrows) suggestive of MCKD.*

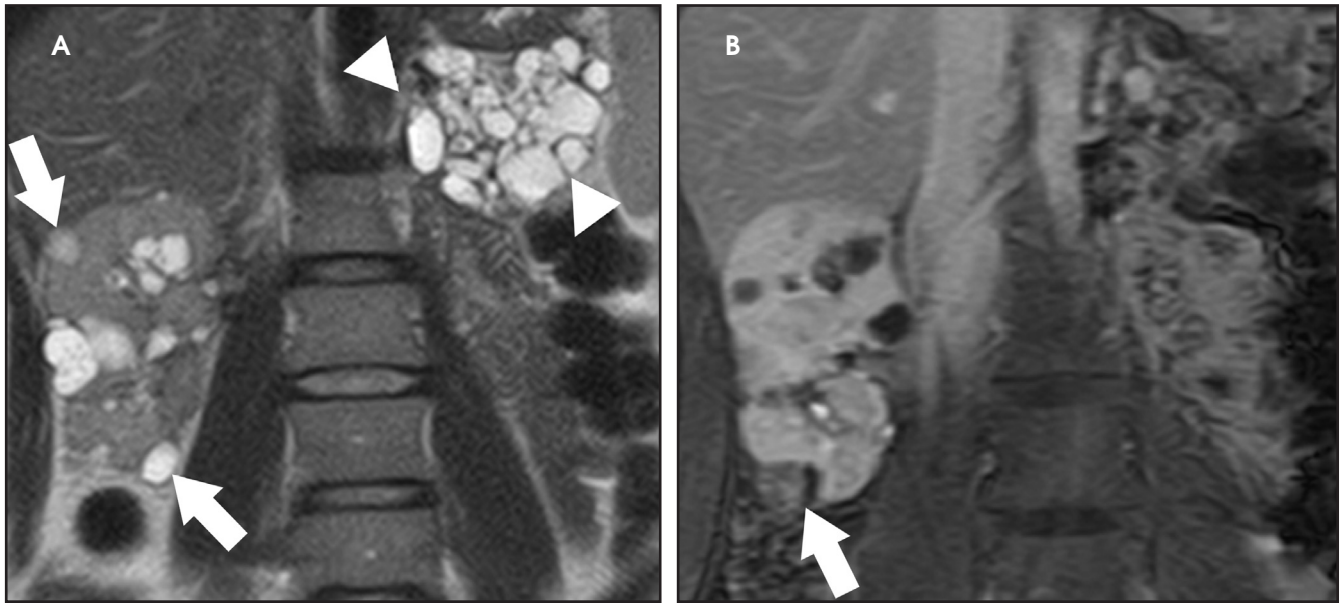

FIGURE 3. *A 24-year-old woman with von Hippel-Lindau disease. Coronal T2- weighted (A) and gadolinium-enhanced (B) MR images show multiple simple and complex cysts and enhancing masses (arrows) in the right kidney. Also note multiple cysts in the pancreas (arrowheads). This patient is status post-left nephrectomy as she had multiple renal carcinomas in the left kidney.*

growth of tubular epithelial cells and uncontrolled cyst formation due to increased intratubular fluid secretion.[4, 7, 8]

Imaging studies not only help in the diagnosis but also play an important role in the assessment of complications and long-term follow-up.[9, 10] At CT/MRI, the presence of bilateral enlarged kidneys containing innumerable simple and hemorrhagic/proteinaceous cysts is typical of ADPKD (Figure 1).[1] Extra-renal manifestations of ADPKD include hepatic, pancreatic, splenic, and seminal vesicle cysts, colonic diverticula, aortic and intra-cranial arterial aneurysms, and abdominal wall hernias. About 45 % of patients will develop end-stage renal disease by the age of 60 years. Novel drugs such as vasopressin receptor blockers and mammalian target of rapamycin (mTOR) inhibitors (for example, sirolimus) are shown to decrease the rate of cyst growth and halt disease progression[11]. MR imaging based renal cyst volumetry is an important tool in monitoring disease progression and assessing treatment response before renal function begins to decline.[9, 12, 13] Continued increase in total kidney and cyst volume indicates progression of disease. There is no evidence of increased risk of renal cell carcinoma in patients with ADPKD.[14]

Medullary cystic kidney disease

Medullary cystic kidney disease (MCKD) is a chronic, progressive kidney disease characterized by bilateral, multiple medullary cysts and tubulointerstitial nephropathy in normal to small-sized kidneys.[15] While MCKD type 1 is caused by mutations of the

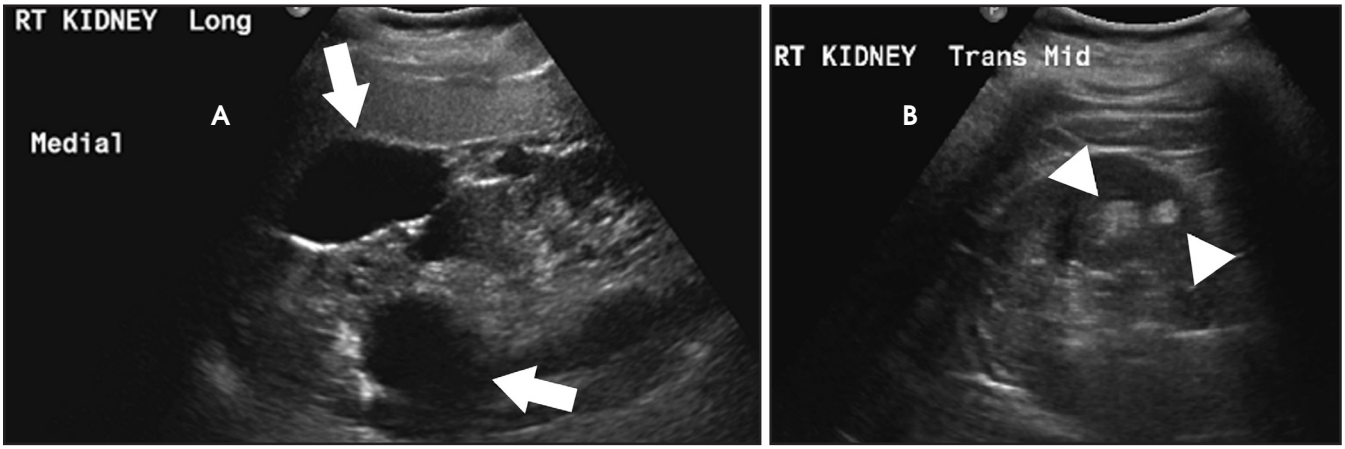

FIGURE 4. *A 42-year-old man with tuberous sclerosis. Longitudinal (A) and transverse (B) ultrasound images of the right kidney demonstrate multiple cysts (arrows) and angiomyolipomas (arrowheads) consistent with the diagnosis of tuberous sclerosis. The left kidney was removed after spontaneous rupture of an angiomyolipoma*

MCKD1 gene (located at chromosome 1q21), type 2 disease is caused by mutations of the MCKD2 gene (located on chromosome 16p12 that encodes for the uromodulin protein).[1,16] Uromodulin protein plays an important role in the formation of normal adhesion signaling complexes in renal tubules. Abnormal function due to gene mutations leads to ciliary dysfunction, which in turn causes medullary cysts.[16,17] Clinically, MCKD patients present with polyuria, polydipsia, hyperuricemia, and slowly progressive renal parenchymal disease leading to end-stage renal disease.[18,19] Imaging studies play an adjuvant role in the diagnosis of MCKD as family history, clinical features, and laboratory findings are the mainstay of diagnosis.[1,20] Although the presence of medullary cysts supports the diagnosis of MCKD, this is not essential. At imaging, the kidneys are small to normal sized and show bilateral, multiple cysts of varying sizes at the medulla or cortico-medullary junction in bilaterally (Figure 2).[21] Renal transplantation is the definitive treatment and the cysts are not known to recur in transplanted kidneys.[1, 22]

von Hippel-Lindau disease

von Hippel-Lindau (VHL) disease is an autosomal dominant, inherited multisystem tumor syndrome characterized by the development of benign and malignant neoplasms of multiple organs. The disease results from inactivating mutations of the VHL tumor-suppressor gene (located at chromosome 3p25 and encoding pVHL protein).[23, 24] The main function of the pVHL is proteosomal degradation of hypoxia inducible factor (HIF), which is involved in homeostasis and oxygen sensing mechanism. Uninhibited up-regulation of HIF and downstream effectors in VHL patients results in uncontrolled cell proliferation and marked angiogenesis resulting in the development of hypervascular tumors.[25] In addition, pVHL plays a seminal role in renal ciliogenesis, ciliary assembly, and function; inactivation of this protein causes deranged ciliary functions that cause abnormal proliferation of renal epithelium.[26, 27] Up to 65% of VHL patients may develop renal manifestations, which include simple and complex cysts and multiple, bilateral clear cell renal cell carcinomas.[25] Common extra-renal tumors include central nervous system hemangioblastomas, retinal angiomas, pancreatic cysts and tumors, and pheochromocytomas.[25] The age of onset of RCCs in VHL patients is much earlier than in sporadic cases of RCCs.[28]

At imaging, the presence of multiple simple and complex renal cysts interspersed with complex cystic and solid enhancing renal masses is characteristic of VHL (Figure 3).[25] Multiple pancreatic cysts are commonly identified in all patients with renal findings. Although some cysts undergo involution overtime, others may grow continuously. Management options for RCCs include continued surveillance and nephron-sparing procedures such as partial nephrectomy or image-guided radiofrequency/cryo ablation. While RCCs measuring more than 3 cm in maximal diameter are usually treated, patients with smaller tumors typically undergo periodic imaging surveillance.[29]

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant condition characterized by both renal and extra-renal manifestations.[30] Renal involvement is seen in about 50-60% of patients, which include renal cysts (14-32%) and angiomyolipomas (30-40%).[31] Central nervous system lesions including multiple cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, and white matter abnormalities are the common extra-renal manifestations in TSC patients. Inactivating mutations of TSC1 gene (located at chromosome 9q34 that encodes hamartin) and/or TSC2 genes (located at chromosome 16p13 that encodes hamartin)[30-32] are responsible for the development of TSC. Tuberin-hamartin protein complex plays an important role in controlling cell growth and proliferation and functions as a tumor suppressor by suppressing mammalian target of rapamycin (mTOR); dysfunction of this protein

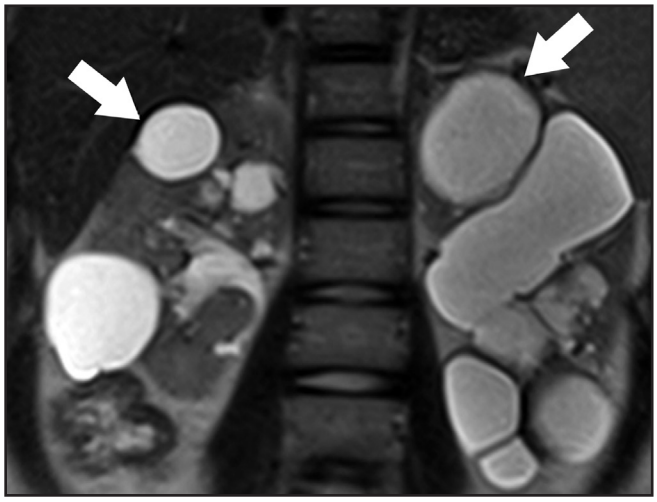

FIGURE 5. *A 19-year-old woman with tuberous sclerosis. Coronal T2-weighted MR image shows multiple cysts (arrows) in bilateral kidneys without angiomyolipomas.*

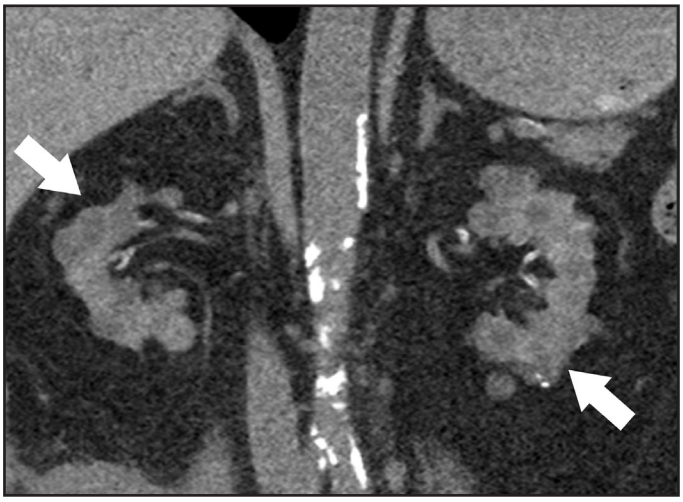

FIGURE 6. *Acquired cystic kidney disease (ACKD) in a 54-year-old man. Coronal unenhanced CT image shows bilateral small kidneys with multiple cysts (arrows) consistent with ACKD.*

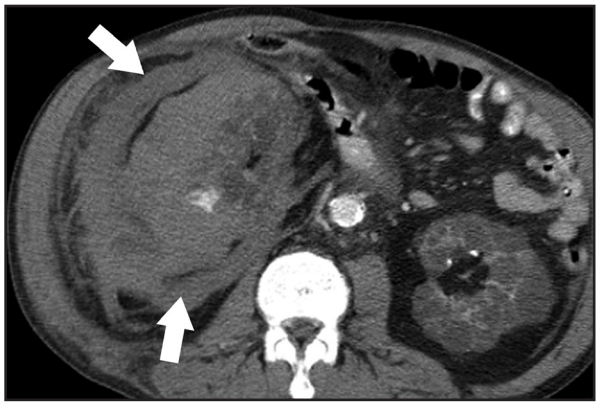

FIGURE 7. *Spontaneous perinephric hemorrhage in a 73-year-old man with known acquired cystic kidney disease. Axial contrast-enhanced CT image demonstrates multiple renal cysts and right perinephric and subcapsular hematoma (arrows) compressing the renal parenchyma.*

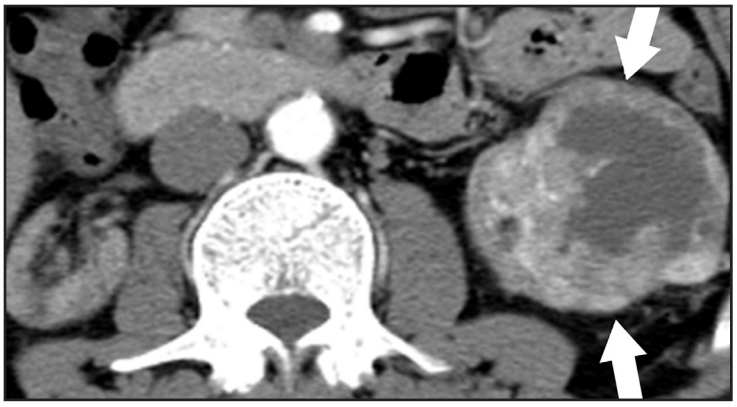

FIGURE 8. *Renal cell carcinoma in an 84-year-old man with acquired cystic kidney disease. Axial contrast-enhanced CT image shows a heterogeneously enhancing mass in the left kidney (arrows) consistent with renal cell carcinoma.*

results in ciliary dysfunction and uncontrolled activation of mTOR leading to the formation of angiomyolipomas and renal cysts.[33, 34]

At cross-sectional imaging, multiple renal cysts intermixed with angiomyolipomas involving bilateral kidneys is the typical appearance of TSC on cross-sectional imaging (Figures 4 and 5).[1,35] Interestingly, some patients may develop only simple cysts while others may have AMLs only; however, both lesions may manifest in childhood and increase in size and number as patients grow older. There is no increased risk of malignancy per se in TSC patients; however, RCC occur at a younger age in comparison to general population.[35]

Non-hereditary cystic kidney diseases

Acquired cystic kidney disease

Acquired cystic kidney disease (ACKD) is characterized by the development of bilateral, multiple renal cysts (three or more per kidney) in patients with end-stage renal disease (ESRD) without any known hereditary cystic renal disease.[36] Although ACKD is strongly associated with long-term hemodialysis, at least 8-13% of patients develop cysts before the initiation of dialysis.[36] Compensatory hypertrophy of the functioning nephrons in ESRD patients is the initial event in ACKD; this leads to stimulation of various mitogenic factors that cause hyperplasia of renal tubular epithelium, increased fluid production resulting in multiple renal cyst formation.[37] Additionally, uncontrolled activation of growth factors and proto-oncogenes result in the development of renal cell carcinoma.[14, 38]

Ultrasound is the primary modality in the diagnosis of ACKD and it typically demonstrates small echogenic kidneys with multiple cysts bilaterally. At CT/MRI, bilateral small-sized kidneys with multiple cysts of varying sizes are the characteristic appearance of ACKD (Figure 6).[1,36] Complications of ACKD include hemorrhage into the cysts, spontaneous cyst rupture resulting in perinephric hematoma, cyst infection, ureteral stones and development of renal

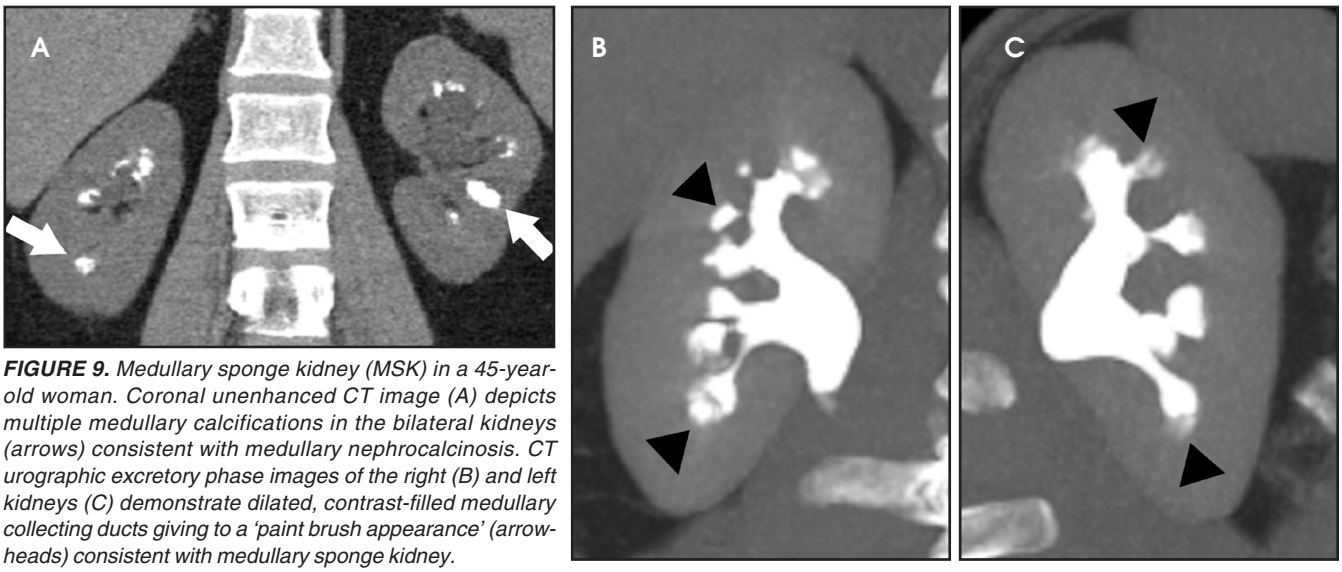

FIGURE 9. *Medullary sponge kidney (MSK) in a 45-year-old woman. Coronal unenhanced CT image (A) depicts multiple medullary calcifications in the bilateral kidneys (arrows) consistent with medullary nephrocalcinosis. CT urographic excretory phase images of the right (B) and left kidneys (C) demonstrate dilated, contrast-filled medullary collecting ducts giving to a 'paint brush appearance' (arrowheads) consistent with medullary sponge kidney.*

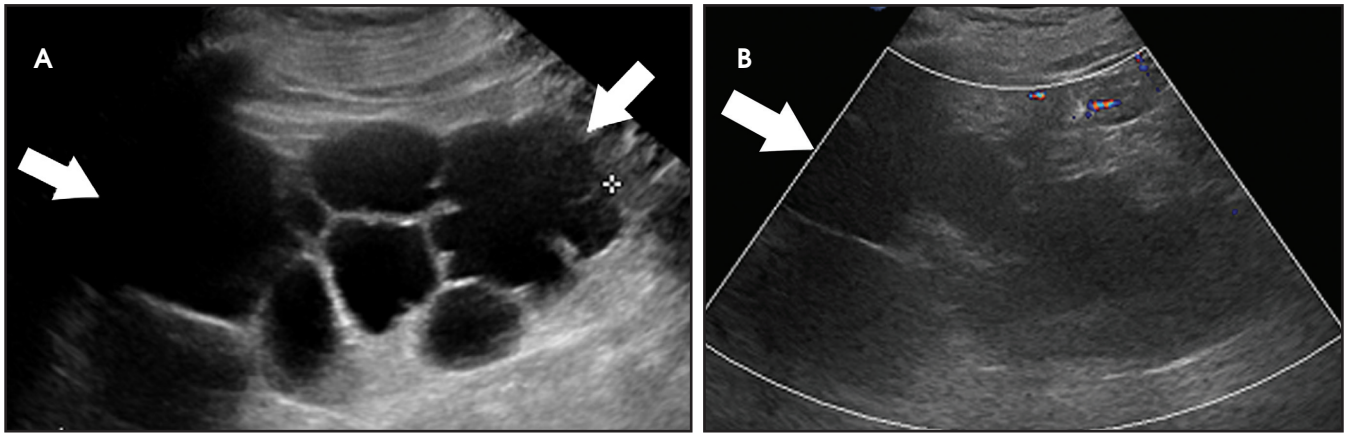

FIGURE 10. *Multicystic dysplastic kidney (MCDK) in a 53-year-old man. Ultrasound (A) and color Doppler (B) images of the right kidney show multiple cysts replacing the entire renal parenchyma (arrows) without any identifiable intrarenal vessels or pelvicalyceal system consistent with the diagnosis of MCDK.*

cell carcinoma (up to 7% of patients) (Figure 7).[36, 37] ACKD-associated RCC and clear cell papillary RCC associated with ESRD are the two common histologic subtypes of RCCs; among them, ACKD-associated RCC is the most common and most aggressive form (Figure 8).[39] Mostly RCCs develop within or around a preexisting cystic lesion, thus making regular US follow-up of these lesions is very important.[36] Although cysts in native kidneys regress in time after renal transplantation, solid neoplasms may show a more aggressive course secondary to immunosuppression.[36]

Medullary sponge kidney

Medullary sponge kidney (MSK) is a developmental anomaly that results from diffuse or focal ectasia and cystic dilatation of the collecting ducts in the renal pyramids. [40] It is hypothesized to result from disruption of the interface between the developing ureteral bud and metanephric blastema during embryogenesis.[40] Most of the patients are asymptomatic; renal colic, hematuria, recurrent urinary tract infections are common presenting symptoms in select symptomatic patients. At intravenous urography, the characteristic 'paint brush' appearance is due to the pooling of contrast, and linear striations radiating from the calyces.[41,42] On ultrasound, the medullary pyramids appear uniformly hyperechoic due to the deposition of calcium in the affected tubules.[1, 43] On unenhanced CT, the presence of medullary nephrocalcinosis is commonly identified and CT urography demonstrates 'papillary brush' morphology and stones within the dilated collecting ducts (Figure 9).[41, 44] MSK has an excellent long term prognosis; however complications of recurrent urinary tract obstruction and infections may cause progressive renal failure.[45]

Multicystic dysplastic kidney

Multicystic dysplastic kidney (MCDK) is a non-hereditary developmental condition that results from urinary tract obstruction during embryogenesis with subsequent abnormal metanephric-mesenchymal differentiation.[46,47] Flank pain, palpable mass and recurrent UTIs are common presenting symptoms. Imaging

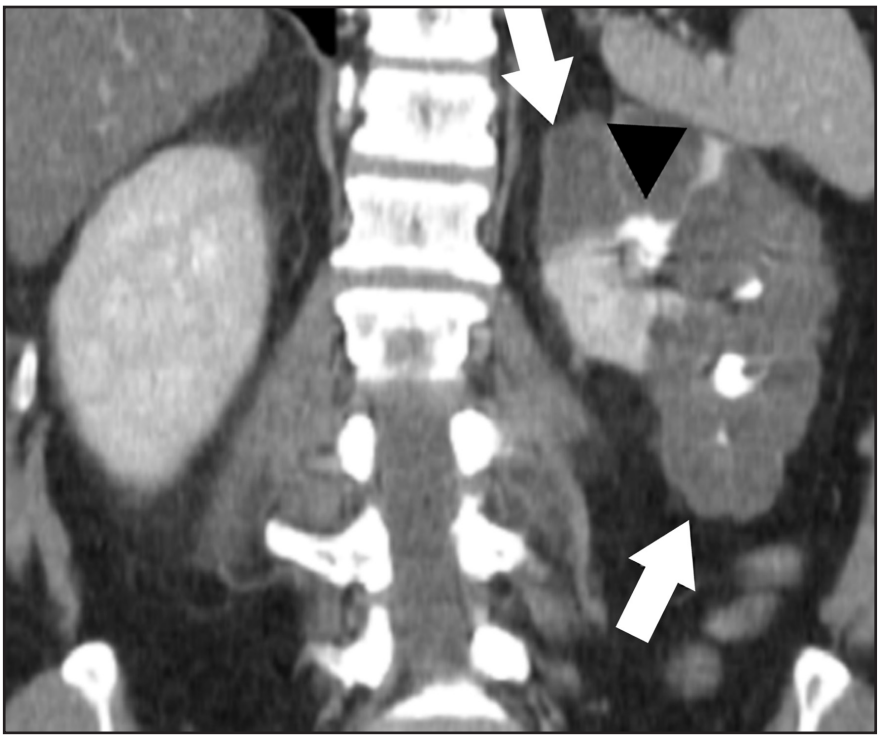

FIGURE 11. *Localized cystic kidney disease (LCKD) in a 36-year-old man. Coronal contrast-enhanced CT image shows multiple cysts, almost involving the entire left renal parenchyma however, there is normal contrast excretion into the collecting system (arrowheads) consistent with localized cystic kidney disease. These cysts were unchanged in appearance for prior 10 years.*

appearance of MCDK may vary depending on the age of the patients. Multiple, noncommunicating cysts in an enlarged, non-reniform shaped kidney without any functioning renal parenchyma is the typical appearance of MCDK in children.[48] In adult patients, MCDK may appear as a multiloculated cystic mass mimicking a cystic neoplasm; however, a nonfunctioning kidney with peripherally located multiloculated cysts and absence of ipsilateral renal vessels, pelvicalyceal system, and ureter favor the diagnosis of MCDK (Figure 10).[1] MCDK follows a benign course and the dysplastic kidney involutes over time.[46,49]

Localized renal cystic disease

Localized renal cystic disease (LRCD) is a rare, acquired, maldevelopmental condition characterized by multiple cysts replacing a variable portion of the kidney or the entire kidney with the cysts being separated by normal (or atrophic) renal tissue.[50, 51] Clinically, the affected individuals present with hematuria, hypertension, flank pain and palpable abdominal mass. At cross-sectional imaging, LRCD is characterized by conglomerate mass of multiple simple cysts involving one kidney, separated by normal / atrophic renal parenchyma (Figure 11).[50, 52] Differential diagnoses includes ADPKD, cystic renal tumor, and MCDK. While the presence of renal vessels and normal contrast excretion separates it from MCDK, unilaterality and the absence of extra-renal manifestations such as hepatic cysts differentiates it from ADPKD. Evaluation of entire kidney in coronal and sagittal planes helps in identification of normal renal parenchyma of LRCD from thickened septations of cystic renal neoplasms.[1] LRCD is a benign, nonsurgical condition that only requires imaging follow-up.[50]

Diagnosis of adult renal cystic disease: A practical approach

Renal size (large vs. normal vs. small), location and laterality of the cysts (cortex vs. medulla; unilateral vs. bilateral), and associated findings in other organs will help in making a definitive diagnosis in an adult patient with multiple renal cysts. Bilateral enlarged kidneys with multiple hemorrhagic and non-hemorrhagic cortical cysts with associated hepatic cysts are typical of ADPKD. Multiple, bilateral medullary cysts in small to normal sized kidneys in appropriate clinical setting favor the diagnosis of MCKD. Bilateral normal to mildly enlarged kidneys with complex renal cysts and multiple enhancing renal masses in conjunction with pancreatic cysts, central nervous system hemangioblastomas are characteristic of VHL. Multiple, bilateral renal angiomyolipomas intermixed with renal cysts in normal to enlarged kidneys is typically seen in Tuberous Sclerosis Complex patients. Bilateral small kidneys with multiple cysts in patients with end stage renal disease is diagnostic of ACKD. Medullary nephrocalcinosis with or without associated cystic dilatation of medullary collecting ducts in bilaterally small to normal sized kidneys is typically seen in MSK patients. Nonfunctioning unilateral kidney with multiloculated appearance and without identifiable renal vessels and pelvicalyceal system is characteristically seen in MCDK. Unilateral or segmental disease with conglomerate renal cysts intervening with normal or atrophic renal parenchyma that demonstrate normal contrast excretion is characteristic of LRCD. Among all, VHL and ACKD have significantly increased risk of renal cell carcinoma and require long-term surveillance.

Conclusion

There is a broad spectrum of hereditary and non-hereditary disorders that cause renal cystic disease in adults. Recent advances in the field of genetics and pathology have thrown fresh light on pathogenesis of some of these disorders leading to development of novel drugs aimed at halting disease progression. Cross-sectional imaging studies not only aid in the detection and differentiation of various chronic adult renal

cystic diseases but also play a significant role in the surveillance and follow-up of patients. Improved awareness of adult renal cystic diseases and familiarity with their cross-sectional imaging findings permit appropriate diagnosis and patient management.

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