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Urologic Diseases Germane to the Medical Renal Biopsy: Review of a Large Diagnostic Experience in the Context of the Renal Architecture and Its Environs

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Abstract: The kidney is one of the most complicated organs in development and is susceptible to more types of diseases than other organs. The disease spectrum includes developmental and cystic diseases, involvement by systemic diseases, iatrogenic complications, ascending infections and urinary tract obstruction, and neoplastic diseases. The diagnosis of kidney disease is unique involving 2 subspecialties, urologic pathology and renal pathology. Both renal and urologic pathologists employ the renal biopsy as a diagnostic modality. However, urologic pathologists commonly have a generous specimen in the form of a nephrectomy or partial nephrectomy while a renal pathologist requires ancillary modalities of immunofluorescence and electron microscopy. The 2 subspecialties differ in the disease spectrum they diagnose. This separation is not absolute as diseases of one subspecialty not infrequently appear in the diagnostic materials of the other. The presence of medical renal diseases in a nephrectomy specimen is well described and recommendations for reporting these findings have been formalized. However, urologic diseases appearing in a medical renal biopsy have received less attention. This review attempts to fill that gap by first reviewing the perirenal anatomy to illustrate why inadvertent biopsy of adjacent organs occurs and determine its incidence in renal biopsies followed by a discussion of gross anatomic features relevant to the microscopic domain of the medical renal biopsy. Unsuspected neoplasms and renal cysts and cystic kidney diseases will then be discussed as they create a diagnostic challenge for the renal pathologist who often has limited training and experience in these diseases.

Key Words: cystic kidney disease, renal cysts, renal cell carcinoma, renal adenoma, renal anatomy

(*Adv Anat Pathol* 2018;25:333–352)

The kidney serves many functions critical to homeostasis including blood filtration, volume control, and secretion and reabsorption of electrolytes, small molecules and proteins. This complexity of function is paralleled in an elegantly organized structure.[1,2] It is one of the most anatomically complicated organs and the organ system most prone to malformations that affect ~10% of the population.[3] The kidneys are vulnerable to hematogenous assault from a variety of systemic diseases, especially hypertension and diabetes, and iatrogenic therapies or exogenous exposures. Its lower urinary output passes through multiple organs and is open to the external environment potentially leading to obstructive complications and retrograde infections.

The diagnosis of kidney disease is also complex. Many medical diseases are championed by renal pathologists who rely upon a medical renal biopsy as their diagnostic modality. They extrapolate findings from a tiny tissue sample to the entirety of both kidneys although the possibility of unilateral or segmental disease must be entertained. Conversely, surgical and urologic pathologists largely rely upon a copious tissue sample, a partial or complete nephrectomy, to characterize a disease that is often unilateral in nature.

Renal pathologists and surgical pathologists have different requisite gross and histologic understanding of the kidney because of the divergent specimen types and disease spectrum they encounter. Several recent publications have highlighted important medical renal diseases present in a tumor nephrectomy that may convey greater prognostic importance than the indication for nephrectomy.[4,5] Conversely, a medical renal biopsy may reveal a urologic disease normally diagnosed on a nephrectomy specimen or at autopsy.

This review initially focuses upon architectural features of the kidney and its environs whose understanding may explain the occasional occurrence of nonrenal organs in a renal biopsy and may enhance insight into renal anatomy-related nonrepresentative biopsy findings. The frequency of inadvertent biopsy of nonrenal organs was assessed by searching the Arkana Laboratories data base to identify biopsies that included liver, spleen, adrenal, pancreas, small bowel, and colon. This section is followed by a discussion of 2 urologic diseases, herein defined as a disease in which a nephrectomy is required to fully understand, that may appear in a medical renal biopsy. This includes (1) cysts and cystic kidney diseases and (2) renal neoplasms. The frequency of encountering a renal cyst or an incidental neoplasm was assessed by searching the Arkana Laboratories data base for key terms cysts, multicystic and polycystic, and carcinoma, adenoma, papillary, metastatic, lymphoma and leukemia, respectively. The reports were reviewed for pertinent demographic and clinical information. It is hoped this large biopsy experience will broaden understanding of the full spectrum of kidney diseases encountered in a medical renal biopsy.

RETROPERITONEUM AND PERIRENAL ENVIRONMENT

The kidneys reside in the retroperitoneum in close proximity to multiple organs (Fig. 1). The retroperitoneum is divided into 3 fascia-invested compartments: anterior pararenal, perirenal, and posterior pararenal spaces.[6,7] The posterior pararenal space contains fat but no organs. In the

From the Arkana Laboratories, Little Rock, AR.
The author has no funding or conflicts of interest to disclose.
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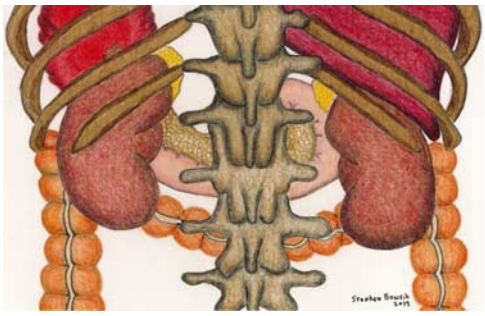

FIGURE 1. This diagram of the abdominal and retroperitoneal organs viewed posteriorly from the perspective of one performing a renal biopsy demonstrates the kidneys and their relationship to neighboring organs.

obese patient the quantity of fat can be formidable complicating performance of a renal biopsy.

The perirenal space is enveloped by the Gerota fascia. It contains the kidneys, ureter and renal pelvis, adrenal glands, aorta, vena cava, and lymph nodes cushioned by perinephric fat. The perirenal space is bounded medially by dense adventitial connective tissues of the aorta and vena cava that impede contralateral spread of perinephric urine leaks, hemorrhage, infection, and neoplastic infiltration.[7]

The anterior pararenal space contains the pancreas and duodenal loop medially and ascending and descending colon laterally (Fig. 1). It thins over the kidneys so that only a thin layer of fat may separate the kidneys from the peritoneum. The kidneys are in proximity to 4 intraperitoneal organs, duodenal loop, pancreas, spleen on the left, and liver on the right (Fig. 1). Knowledge of the perinephric neighborhood is important when performing a renal biopsy as these organs are occasionally sampled. Fortunately, the vena cava and aorta located anterior to the vertebral bodies are usually secure from inadvertent biopsy. In a review of 44,000 Arkana Laboratories medical renal biopsy reports 75 cases (0.17%) contained one or more nonrenal organs (Table 1). Although, complications developing when a wayward needle encounters a perinephric organ appear negligible, the clinician should always be notified of the finding.[8,9]

PERINEPHRIC FAT

The kidney has a 1 to 2 mm dense fibrous capsule investing its peripheral aspects and 2 perinephric fat compartments.[1,3] The peripheral perinephric fat is located between the Gerota fascia and the renal capsule. Its quantity varies substantially between individuals. It can be involved in a variety of inflammatory and neoplastic processes. The perinephric tissue as well as any associated blood in a biopsy merit examination as they may rarely contain important diagnostic findings such as a soft tissue tumor (angiomyolipoma, liposarcoma, etc.), amyloid deposits, or a hematopoietic neoplasm that may not be present in the renal tissue (Figs. 2A, B).

The second perinephric fat compartment is the renal sinus defined as the space between the pelvicalyceal system and the renal parenchyma. The sinus has a complex 3-dimentional structure due to forniceal extensions containing fat and interlobar vessels that invest the pyramids and minor calyces.[10] As the pyramids and minor calyces angle toward the collecting system from the anterior and posterior plane, in a bivalved kidney or in a renal biopsy sinus tissue may appear completely surrounded by renal parenchyma (Figs. 3A, B). Evaluation of the renal sinus is critical in tumor staging as it represents the primary site of extrarenal extension for pediatric and adult renal cancers.[11–13]

Sinus tissue can be distinguished from capsule and perinephric tissue in a renal biopsy. The renal capsule consists of dense fibrous tissue with a laminar organization (Fig. 4A). The peripheral perinephric fat contains small arteries and veins and no nerves. Conversely, sinus tissue contacts directly the parenchyma of the inner medulla or cortical column of Bertin without a fibrous capsule. The sinus contains loose unorganized connective tissue and fat. In contrast to the peripheral perinephric fat, nerves and large arteries, and veins may be present (Fig. 4B).

TABLE 1. Organs Unintentionally Sampled During a Renal Biopsy (Search of 44,000 Renal Biopsies = 0.17% Incidence)

Single Organ = 69		Multiple Organs = 6	
Liver	20	Small bowel and spleen	2
Colon	12	Pancreas and small bowel	1
Small bowel	12	Pancreas and liver	1
GI, NOS	11	Liver and colon	1
Spleen	8		
Pancreas	5		
Adrenal	1		
Hyaline cartilage	1		

GI indicates gastrointestinal; NOS, otherwise specified.

RENAL LOBAR ARCHITECTURE

The kidney has a lobar architecture with an average of 14 lobes per kidney. Each lobe consists of a tapering cone of renal medulla surrounded by a cap of renal cortex.[1,3] The lateral cortical interfaces of a lobe form the columns of Bertin whose glomeruli drain in opposite directions. Renal lobes may be single (simple) or fused (compound). Compound pyramids drain more than one lobe. They are concentrated at the poles and have a concave pelvic surface. This architecture results in susceptibility to intrarenal reflux with infection and/or obstruction because their ducts of Bellini open under pressure in contrast to simple pyramids whose ducts close. As the lower pole is usually the target of a medical renal biopsy, in reflux-related disease biopsy findings may not be representative of the kidney elsewhere or the contralateral kidney. Furthermore, 2 separate cores of cortex can look radically different if they sample adjacent simple and compound pyramids in a reflux-related disease (Figs. 5A, B).

RENAL LYMPHOVASCULAR CONNECTIONS

Vascular disease is the most common cause of acute and chronic kidney injury. Vascular-related lesions may be focal in a biopsy or affect the entire specimen. The vascular supply to kidney provides an anatomic basis for these possibilities. There are many variations in renal artery and vein organization but a few generalizations apply.[14,15] The main renal artery divides into 5 segmental arteries. An upper pole and lower pole segmental (polar) artery supplies the anterior and posterior of each pole. A polar artery may also arise also directly from the aorta to supply a polar region. This occurs in 20% to 30% of patients.

All renal arteries are end arteries lacking collateral connections. Therefore, the size of a vascular lesion is a

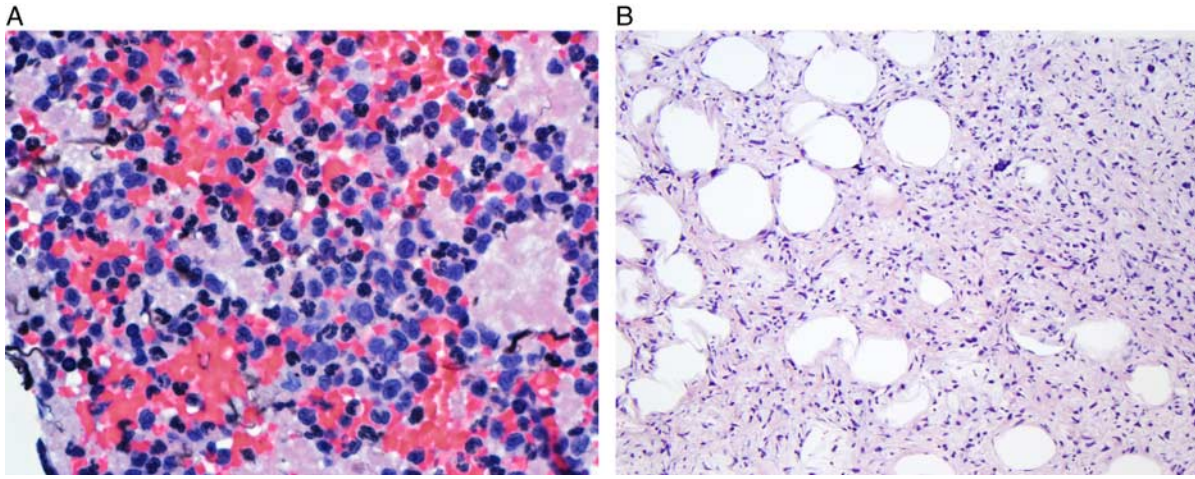

FIGURE 2. A, This blood clot associated with a renal biopsy contained a leukemic infiltrate consistent with chronic myelomonocytic leukemia. Leukemic cells were not present in the renal biopsy core which showed lysozyme-induced acute kidney injury. B, This is an unsuspected perirenal liposarcoma identified in a biopsy performed for chronic kidney disease.

guide to the caliber of artery affected. This can be estimated when the entire kidney is available.[3] In a renal biopsy the extent of renal involvement cannot be precisely determined but inferences can be made about the artery involved. Focal or multifocal cortical infarction with portions of uninvolved cortex indicates peripheral interlobular artery disease because an interlobular artery branches one or more times in the cortex (Fig. 6). Conversely, transcortical infarction, especially if associated with medullary infarction, implicates involvement of an arcuate artery or larger artery. An isolated inner medullary infarct without cortical involvement results from spiral artery occlusion. Spiral arteries arise from interlobar arteries and supply the papillary tips.

A vascular lesion in a renal biopsy, even if diffuse, may result from isolated polar artery lesion and may not be representative of the kidney(s) elsewhere even when multiple cores are affected. An example is a transplant biopsy with total infarction in a patient with only mild renal impairment suggesting that a polar segmental artery was missed during harvesting or transplantation. Conversely, multiple cores sampling adjacent arterial beds may show different findings, normal and infarcted or ischemic, if an occlusive lesion involves one artery bed but not an adjacent one.

Renal veins, unlike veins in other organs, lack a smooth muscle media, in effect, resembling dilated capillaries (Fig. 7). This may facilitate accommodation of their massive flow demands. The kidneys comprise <1% of the body weight yet receive 20% of the cardiac output. The renal venous return is voluminous as 99% of the glomerular filtrate is reabsorbed.

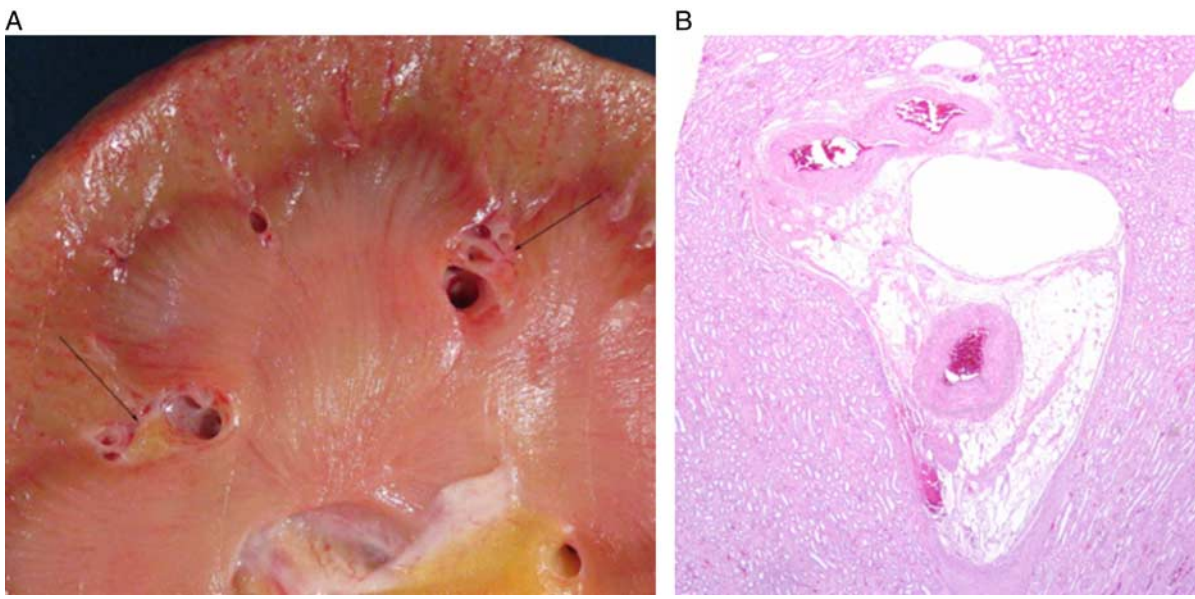

FIGURE 3. A, This bivalved kidney shows sinus forniceal extensions in cross section (arrows) surrounded by renal parenchyma. Notice the fused renal pyramids with their mutual concave papilla. B, This sinus forniceal extension is surrounded by cortex at the top and renal medulla on both sides.

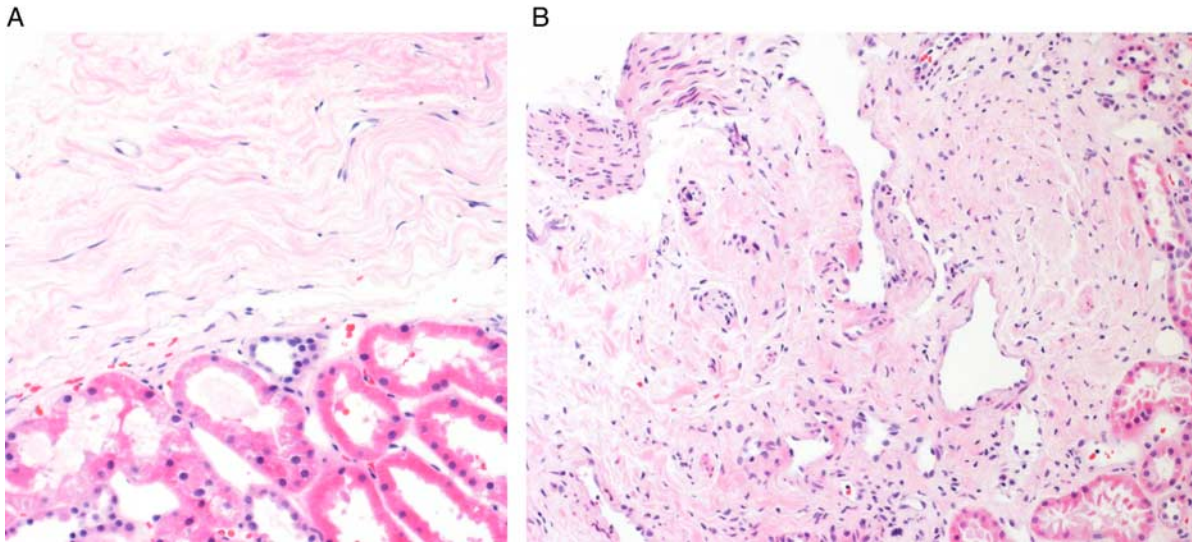

FIGURE 4. A, The renal capsule is composed of lamellar fibrous tissue with occasional small vessels. B, This forniceal portion of the renal sinus contains unorganized connective tissue, a medium sized vein and small nerve (upper left). It interfaces with tubules of a column of Bertin (lower right).

Venous-related disease is unusual in a renal biopsy as renal veins, unlike renal arteries, have extensive collateral connections. However, with main renal vein thrombosis bland fibrin thrombi and/or neutrophils may occasionally be seen in glomerular capillaries.

Knowledge of venous anatomy is important for surgical pathologists when evaluating a renal neoplasm for staging purposes.[13] The interlobar veins enter the renal sinus between renal pyramids. The posterior sinus veins cross over the minor calyces anterior to the renal pelvis and converge with the anterior veins to form a venous plane (Fig. 8). The largest sinus veins are usually 1 to 2 cm in diameter but can become much larger when involved by tumor. As most renal cell carcinomas (RCCs) metastasize by extension into these large veins, examination of the anterior venous plane is required for tumor staging.[13]

Tumor dissections along the anterior venous plane led to the recognition of retrograde venous invasion.[16] Retrograde venous invasion occurs when the main renal vein is occluded by tumor leading to retrograde growth within venous tributaries draining the non-neoplastic cortex (Fig. 9). Tumor can sequentially involve interlobar, arcuate, and interlobular veins. In a bivalved specimen this process is easily mistaken for multiple primary tumors because continuity with the main tumor may not visible due to the circuitous route the veins travel.

The main renal vein is formed by confluence of the segmental veins near the renal hilum.[17,18] It has multiple systemic connections relevant to metastases of renal cancers (Fig. 10). The main renal vein connects to lumbar veins posteriorly, the hemiazygous veins on the left, azygous veins on the right, gonadal, and common iliac veins inferiorly.[19]

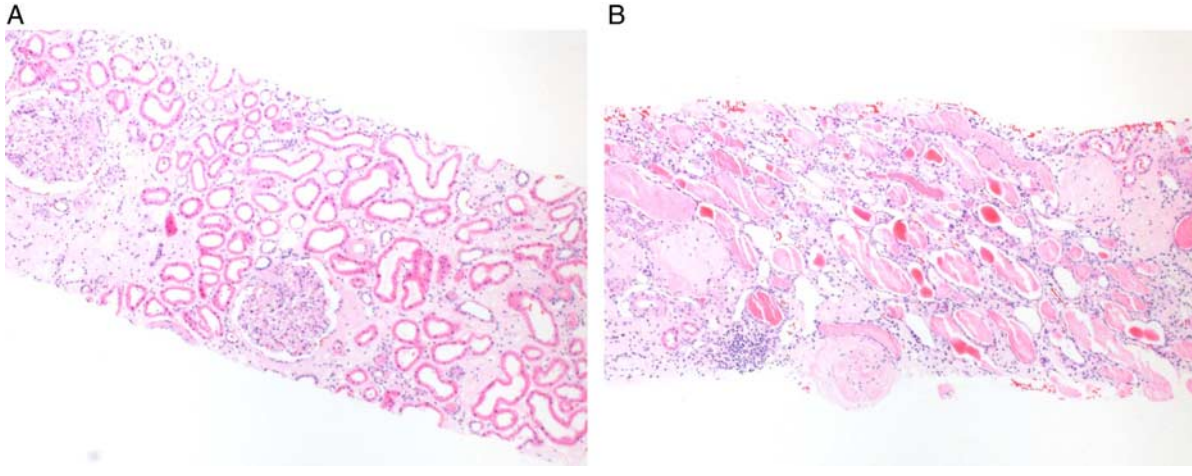

FIGURE 5. A and B, This biopsy with 2 separate cores is from a diabetic patient. It shows acute tubular injury in one core (A) and thyoidization type of chronic tubular injury in the second core (B). This is consistent with biopsy of 2 separate renal lobes, one associated with a normal pyramid and one associated with a refluxing renal pyramid, respectively.

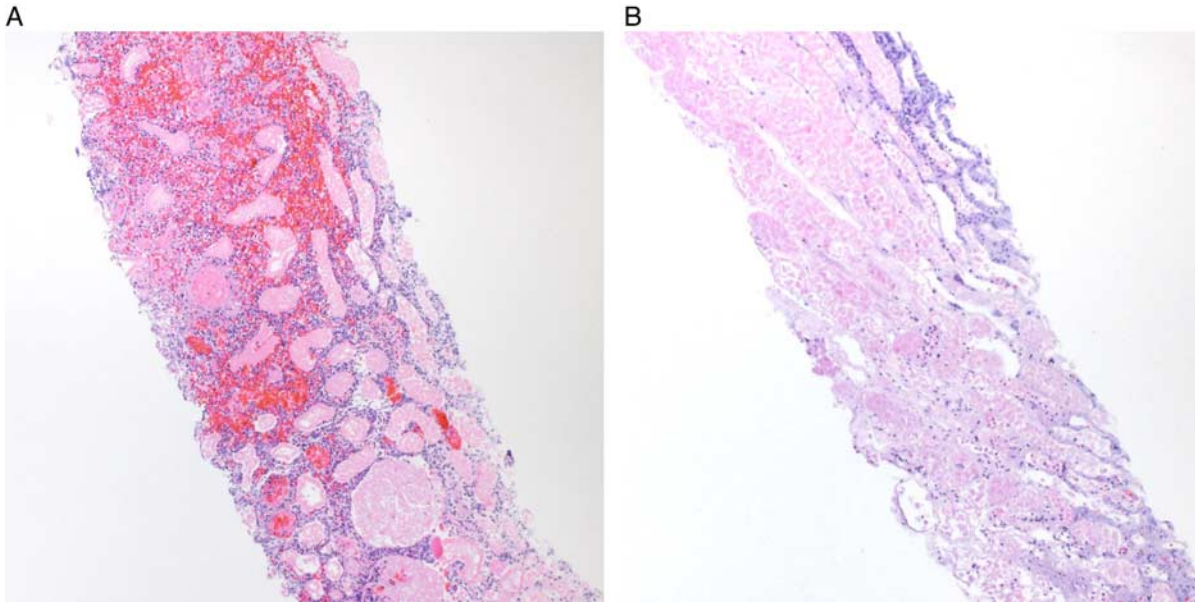

FIGURE 6. A and B, This biopsy with 2 separate cores shows acute cortical infarction (A) and acute medullary infarction (B). This combination implicates an arcuate artery or larger artery occlusion.

The lumbar veins at each intervertebral disk connect to the vertebral venous system, a venous labyrinth with longitudinal sinuses that extends along the entire spinal column. Inferiorly, the vertebral venous system communicates with sacral, pelvic, and prostatic veins. Superiorly, it communicates with the intracranial venous system consisting of the cortical veins, dural sinuses, cavernous sinuses, and ophthalmic veins. The subsequent venous drainage of the intracranial system ultimately flows into the jugular veins and then the superior vena cava.

Batson[20] in 1940 employed intravenous injection with x-rays and demonstrated that the vertebral venous system is a low pressure, large capacitance valve less system that permits bidirectional blood flow. Changes in intracranial pressure due to straining, coughing or sneezing, result in blood flow from intrathoracic, abdominal, and retroperitoneal veins into the vertebral vein and the intracranial venous system. Blood flow reverses repeatedly during the day. Thus, renal cancers can spread to the pelvic bones and organs, the vertebral skeleton, and demonstrate the seemingly paradoxical behavior of bypassing the heart and lungs to metastasize to the skull, brain, and head and neck sites.[20] Batson commented about the vertebral venous system "we have a vast intercommunicating system of veins … constantly and physiologically the site of frequent reversals of flow. During these reversals a pathway up and down the spine exists which does not involve the heart or lungs. It provides a ready vehicle for the explanation of 'aberrant' metastatic patterns."[21]

The kidney has a rich lymphatic drainage that begins in the connective tissue investment of peripheral interlobular arteries and veins.[22] Although cortical lymphatics are

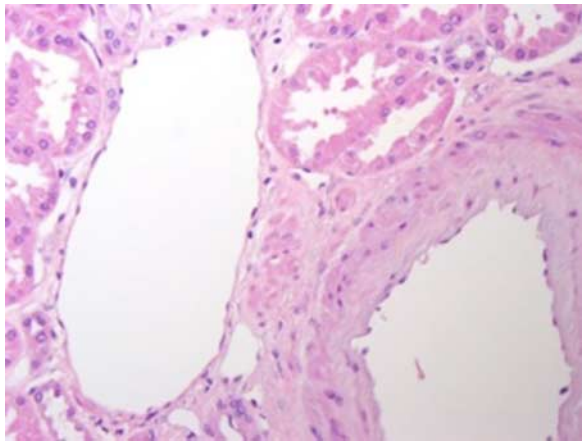

FIGURE 7. This interlobular vein (left) resembles a large dilated capillary since it lacks a smooth muscle media.

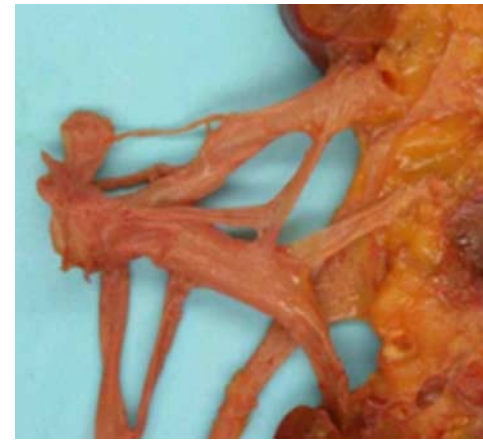

FIGURE 8. This left kidney shows multiple large venous tributaries converging outside of the kidney to form the main renal vein. Notice the many venous interconnections including the adrenal vein (above proximal main renal vein) and also note 2 inferior periureteral (gonadal) venous connections.

FIGURE 9. This is a diagrammatic illustration of retrograde venous invasion. Tumor has entered a large tumor-draining vein with occlusion of the main renal vein. Tumor is shown growing retrograde into veins draining the non-neoplastic cortex mimicking multifocal tumor.

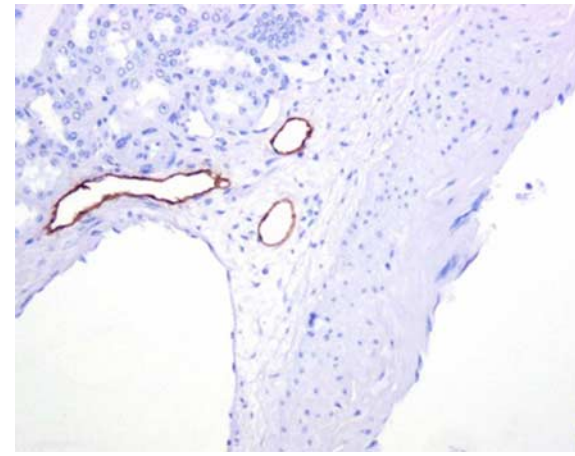

FIGURE 11. Three cortical lymphatics are stained with podoplanin. They resemble capillaries but are much smaller than the corresponding artery and vein. Podoplanin immunoperoxidase stain.

usually smaller than the adjacent veins, they resemble cortical veins and capillaries as they also lack smooth muscle (Fig. 11). Cortical lymphatics drain toward the medulla and enter the sinus. In the normal kidney no, or only rare lymphatics exist among glomeruli, cortical tubules or in the medulla. However, neolymphangiogenesis occurs in these sites with diverse inflammatory processes.[22]

Most lymph exits the renal sinus through the hilum. There are also lymphatics in the pelvic muscularis allowing an alternate pelviureteral flow. The primary locoregional drainage is to the hilar lymph nodes although only 15% to 24% of radical nephrectomies have lymph node tissue identified even when all of the hilar fat is examined histologically.[23–26] Hilar lymph most often goes to one or more nodal stations that surround the aorta and vena cava. From there lymph can follow 3 parallel tracks up or down the aorta and the vena cava as illustrated in the drawing from lymphatic injection studies of Parker in 1935[24] (Fig. 12).

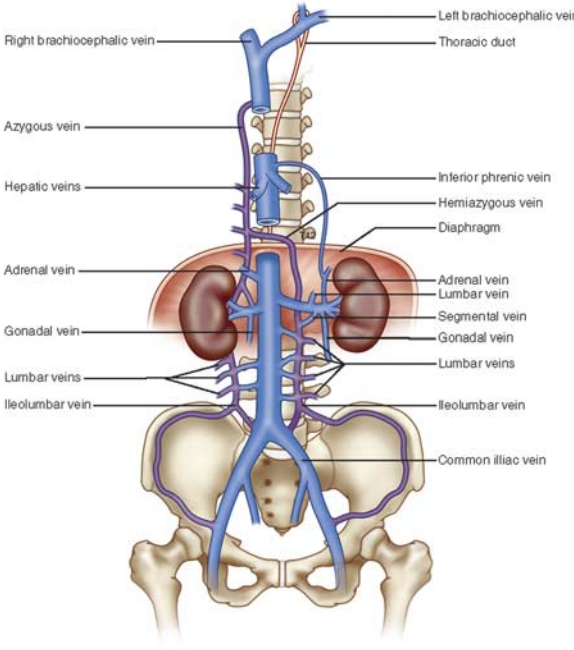

FIGURE 10. This diagram shows the diverse venous interconnections between the renal veins and the hemiazygous and azygous systems and the lumbar veins. These provide avenues for metastatic spread to pelvic and vertebral venous systems and the head and neck (with permission[19]).

Lymphatic metastases are capricious because lymph flow is as well. Lymph may flow to the hilar lymph nodes, bypass the hilar nodes and travel directly to the aorto-caval nodes, or bypass both nodal stations and involve thoracic lymph nodes or pelvic nodes. This explains why only one third of RCC patients with positive locoregional nodes will have positive hilar lymph nodes.[25,26] Lymph node metastases may even proceed directly to the thoracic duct and into the left brachiocephalic vein to become hematogenous. The unpredictability of lymphatic spread may explain the infrequent use of regional lymph node dissection in RCC treatment and sentinel lymph node biopsy in operative staging of RCC which is technically feasible.[27–29]

RENAL CYSTS AND CYSTIC KIDNEY DISEASES

Cysts are the most common cause of a renal mass noted on abdominal imaging.[30–34] Most are benign cysts, but complex cysts and cystic kidney diseases also occur. Cysts may also be encountered as a microscopic finding in a medical renal biopsy. In a search of 44,000 consecutive renal biopsy reports at Arkana Laboratories renal cysts were sufficiently prominent to merit mention in 147 cases (0.3%).

Cysts in a renal biopsy pose a diagnostic challenge as there are so many types of cysts and cystic kidney diseases.[35,36] They include nongenetic and genetic causes. The nongenetic causes include a miscellaneous collection of entities such as simple cortical cysts, acquired cystic kidney disease, isolated polycystic kidney disease and lithium-associated cysts.

Genetic causes fall into 2 broad categories. The first is mutation of one or more "Master" developmental genes that give rise to congenital anomalies of the kidney and urinary tract (CAKUT) of which a cystic kidney is but one type of anomaly.[37–39] These are common occurring in ~10% of the population and accounting for up to 50% of renal failure in children. They present in syndromic and

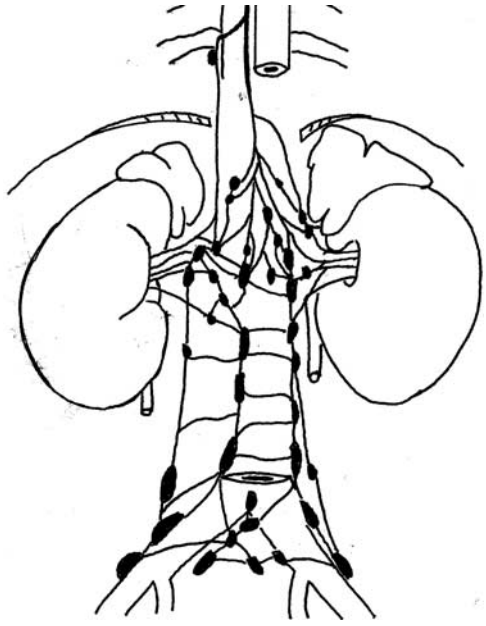

FIGURE 12. This is a diagram of cava and aortic lymph node stations and their interconnections, adapted from Parker's 1935 study.[24]

sporadic contexts, the latter being most common. CAKUT may affect a single kidney-lower urinary tract unit with a completely normal contralateral kidney, or may show bilateral anomalies that differ in type, even with a germline mutation that might be expected to act similarly on both kidney-lower urinary tract moieties (Table 2).

The second genetic cause is mutation of a ciliary gene (>60 genes identified) giving rise to a ciliopathy (Table 3). Ciliopathy genes encode for proteins crucial to the formation and function of the primary cilium of renal tubular cells and extrarenal epithelium.[40–42] The primary cilium is a slender organelle that originates from the basal body and extends from the apical surface of most renal epithelial cells including parietal epithelium. It was long regarded as a vestigial structure but is now known to have critical sensory and cell signaling functions that affect cell differentiation, proliferation, and polarity.

The ciliopathies are clinically and pathologically diverse. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked. The kidneys may be developmentally normal at birth and later develop cysts, or may be are abnormal at birth with cysts and metanephric dysgenesis (renal dysplasia) indistinguishable for some CAKUT

TABLE 2. CAKUT Malformations

Renal agenesis
Renal hypoplasia
Renal dysplasia
Renal fusion, ectopia, and duplication
Ureteral-pelvic junction and uretero-vesical junction obstruction
Vesicoureteral reflux
Ureteral duplication, ectopia, and ureterocele
Bladder extrophy, persistent cloaca and rectal-vesical fistula
Urethral atresia and posterior urethral valves

CAKUT indicates congenital anomalies of the kidney and urinary tract.

TABLE 3. Major Ciliopathies

Autosomal dominant
Autosomal dominant polycystic kidney disease
von Hippel-Lindau disease
Autosomal recessive
Autosomal recessive polycystic kidney disease
Nephronophthisis (+/−renal-retinal dysplasia, +/−Joubert syndrome, +/−Senior Loken syndrome)
Bardet-Beidl syndrome
Meckel-Gruber syndrome
Jeune syndrome
X-linked
Oral-facial-digital syndrome

abnormalities. Some result in a tubulointerstitial nephritis with occasional cysts while others result in cystic kidney disease with a neoplastic diathesis. All have extrarenal components.

The American Academy of Pediatrics, Section of Urology, established terminology for cystic kidneys as shown in Table 4.[43] Notice that a cyst does not need to be spherical or completely enclosed. Nor does it have to be large, only 200 μm or more, the size of an adult glomerulus and Bowman's capsule. This is well below the 1 to 2 mm threshold of for radiographic imaging of a cyst. A cystic kidney does not necessarily connote a cystic kidney disease, that is, a disease related to cysts. Also note that a polycystic kidney is not just a kidney with multiple cysts, rather, it indicates a genetic cystic kidney disease.

Cyst evaluation is most straightforward in a nephrectomy specimen or at autopsy compared with a renal biopsy because the number, location and laterality of cysts, the histology of the cyst lining and the noncystic parenchyma are easily assessed, and the family history is often known. Cysts on a biopsy often elicit more questions than answers because of limited morphologic and clinical data. In general, cysts detected in a pediatric biopsy are more ominous than in an adult because a genetic disease is likely. My approach to the classification of cystic kidneys begins with a topographical approach supplemented by anatomic and clinical information as listed in Table 5. An algorithm for this approach is provided (Table 6).

The cyst topography algorithm was designed for a nephrectomy or autopsy kidney but may also be helpful with a renal biopsy. It does not capture all the nuances and possibilities but provides a starting point. Notice that multiple entities are repeated in first 3 categories, infrequent cysts, unilateral numerous cysts, and bilateral numerous cysts. This was done for 2 reasons. First, there is a spectrum of disease severity for many entities. For instance, renal dysplasia varies from clinically insignificant occasional cysts, to unilateral cysts, to severe lethal bilateral multicystic dysplasia. Second, cyst progression is inherent in several cystic diseases such as acquired cystic kidney disease, autosomal dominant polycystic kidney disease, von Hippel-Lindau disease, tuberous sclerosis complex and in patients on lithium therapy. Initially mild and clinically insignificant cysts may progress over years or decades to cystic kidney disease.

Only a few cystic diseases have both cortical and medullary cysts. This includes acquired cystic kidney disease, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease and lithium-associated cystic disease.[44–59] Cysts limited to the medulla are uncommon but occur in only a few situations, childhood/young adult

TABLE 4. Renal Cystic Disease Nomenclature and Terminology[43]

Renal cyst	An enclosed or communicating segment of nephron or duct dilated to a diameter of 200 μm or more
Cystic kidney	A kidney containing 3 or more cysts
Cystic kidney disease	Morbidity attributable to the presence of renal cysts
Polycystic kidney	A genetically determined cystic lesion of either the autosomal-dominant form or autosomal-recessive form
Multicystic kidney	Multiple cystic lesions; they can be small, segmental, unilateral or bilateral, most often sporadic
Renal dysgenesis	Abnormal development of the kidney in regard to size, shape or structure. Forms of renal dysgenesis include dysplasia, hypoplasia, aplasia, agenesis and dysmorphism
Renal dysplasia	Abnormal metanephric differentiation diagnosed histologically. It may be diffuse, segmental or focal
Renal aplasia	An extreme form of dysplasia in which a nubbin of dysplastic kidney caps a normal or an abnormal ureter
Renal agenesis	Absent kidney
Renal adysplasia	Combined renal agenesis and renal dysplasia, or a hereditary syndrome where either of these findings occur
Renal hypoplasia	A small kidney or segment with less than normal number of nephrons. Dysplastic elements are not present
Dysmorphic kidney	A misshapen kidney and calyceal system. Implies a congenital lesion without any histologic or etiological implications
Acquired cystic kidney disease	The spontaneous, idiopathic, bilateral development of multiple cysts in previously noncystic kidneys
Glomerulocystic kidney disease and glomerulocystic kidney	Glomerular cysts as a dominant finding; glomerulocystic kidney disease is a primary disease; glomerulocystic kidney is a kidney with glomerular cysts but of diverse etiologies
Medullary sponge kidney	A usually sporadic medullary cystic abnormality that is commonly diagnosed by radiology

presentations of autosomal recessive polycystic kidney disease, medullary sponge kidney (history of nephrolithiasis), nephronophthisis, and autosomal dominant tubulointerstitial diseases (formerly known as medullary cystic kidney disease) due to *UROM*, *MUC1*, *REN*, and *HNF1β* mutations.[56–63] Cysts in the latter 2 diseases do not affect all patients. If cysts develop they are usually seen in the advanced stages of disease and rarely present at the time of renal biopsy.

The combination of cysts and solid tumors also has a limited differential although simple cysts and a renal tumor may coincidentally be present.[64–75] There are 3 cystic kidney diseases with a significant neoplastic diathesis acquired cystic kidney disease, von Hippel-Lindau disease, and tuberous sclerosis complex (Table 7). Recently chronic lithium therapy also has been associated with an increased risk of renal neoplasms, both benign and malignant.[74,75] Some would also include autosomal dominant polycystic kidney disease to this list, but evidence is limited and no large population-based studies have been reported to indicate an increased risk of RCC.

TABLE 5. Cyst Classification Data Set

Cyst topography
Number and laterality of cysts
Localized vs. diffuse cysts
Medullary vs. cortical and medullary cysts
Extrarenal findings
Extrarenal malformations
Lower urinary tract abnormalities
Size of the kidneys
Clinical information
Family history of cystic kidney disease
Chronic kidney disease before cyst detection
History of lithium therapy

BOSNIAK CLASSIFICATION OF RENAL CYSTS

A simple cortical cyst is the most common type of renal cyst.[76–78] A simple cyst must be radiologically distinguished from a complex cyst that has septations, calcifications, solid areas, or shows enhancement, findings that may indicate malignancy. This issue is addressed with the Bosniak Renal Cyst Classification.[79–81] In 1986 Bosniak proposed a classification of renal cysts based upon x-ray computed tomography findings into 4 types, types I to IV, intended to distinguish benign and likely benign cysts (type I and II) from cysts suspicious for malignancy (type III) or clearly malignant cysts (type IV). The classification was modified in 1997 with the addition of type IIF (F for follow-up) to reduce the number of benign lesions in the type III category. This classification is widely used by radiologists and urologists to stratify patients into a surgical group (types III and IV) and a nonsurgical group (types I and II), with a third group (type IIF) requiring follow up at 3 to 6 months intervals. Major entities that present as a Bosniak type IIF, III, and IV complex cyst are listed in Table 8.

MOST COMMON RENAL CYSTS

The 4 most common types of cysts encountered in a renal biopsy are simple cysts and cysts developing in acquired cystic kidney disease, autosomal dominant polycystic kidney disease, and chronic lithium therapy (Table 10). There is only one medical renal biopsy study of renal cysts.[48] Liu and colleagues in a review of 720 biopsies found "microcysts" in 21 cases (2.9%). The cysts were regarded as acquired because all patients had chronic kidney disease and autosomal dominant polycystic kidney disease was excluded clinically. The cell lining ranged from flattened to low cuboidal based upon images provided. As no cysts were noted on x-ray computer tomography examination of 20 patients they would not carry a clinical diagnosis of acquired cystic kidney disease. Thus, the presence of cysts on a renal biopsy may indicate a cystic kidney but not necessarily a cystic kidney disease.

TABLE 6. Cyst Topography Algorithm

Unilateral Numerous Cysts						Bilateral Numerous Cysts				
			−Malformations				−Malformation			
Infrequent Cysts			Diffuse				Cortex and Medulla			
+Malf	−Malf	+Malf	LUT Abnormal	LUT Normal	Focal	+Malf	LUT Abnormal	LUT Normal	Medulla	Cysts and Solid
Syndromes: Zellweger Juene Trisomies Ivemark, etc.	Simple cysts	Syndromic dysplasias: Zellweger Juene Trisomies Ivemark, etc.	Sporadic dysplasias	Sporadic dysplasias	Segmental dysplasias	Syndromic dysplasias: Zellweger Juene Trisomies Ivemark, etc.	Sporadic dysplasias	Sporadicdysplasias	Med sponge	ACKD
	ADPKD			ADPKD	Segmental Dysplasia			ADPKD	ARPKD	VHL
	ACKD			ACKD	Localized CKD			ARPKD	NPHP	TSC
	Lithium VHL TSC			Lithium VHL TSC	MEST family Cystic RCCs			Lithium VHL TSC	ADTID	

ACKD indicates acquired cystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; ADTD, autosomal dominant tubulointerstitial disease; ARPKD, autosomal recessive polycystic kidney disease; CKD, cystic kidney disease; LUT, lower urinary tract; Malf, extrarenal malformations; Med, medullary; MEST, mixed epithelial and stromal family of tumors; NPHP, nephronophthisis; RCC, renal cell carcinoma; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau disease.

A simple cyst (type 1 Bosniak cyst) is usually asymptomatic, unilocular and exophytic.[76–78] Occasionally it may have thin septa (type 2 Bosniak cyst). They are uncommon before the age of 40 but increase in prevalence, number and size with advancing age. Half of individuals over the age of 50 have a simple cyst and one third will have multiple simple cysts. Historically simple cysts have been regarded as incidental. Recent evidence, however, indicates a frequent association with hypertension, small kidneys and chronic kidney disease especially when large and multiple.[82]

A simple cyst is lined by a uniform flattened to low cuboidal epithelium, or if large, may have no cell lining (Fig. 13). A small simple must be distinguished from an empty Bowman's capsule or a cortical vein which may appear similar because of their flattened cell lining. Cysts identical to simple cysts are seen in autosomal dominant polycystic kidney disease and acquired cystic kidney disease but cysts with other types of cell lining are also present. In general, in an adult over the age of 40 autosomal dominant polycystic kidney disease is unlikely if only 1 to 2 radiologically identified cysts are present. Acquired cystic kidney disease can be excluded if advanced chronic kidney disease is absent.

Acquired cystic kidney disease is defined as the presence of 3 or more renal cysts in a patient with advanced chronic kidney disease not due to a cystic kidney disease.[44–49] In end stage kidneys the incidence of acquired cystic kidney disease, and the number and size of cysts increase with duration of dialysis. By 10 years 90% of patients will have acquired cystic kidney disease. However, up to 8% of patients may develop acquired cystic kidney disease before initiation of dialysis. Thus, acquired cysts are not uncommon in a medical renal biopsy in a patient with chronic kidney disease.

Cysts in acquired cystic kidney disease develop in both cortex and medulla, and involve proximal and distal tubules, and collecting ducts. By definition, they are associated with significance tubulointerstitial scarring (Figs. 14A–C). The cyst lining is morphologically diverse ranging from a flattened or cuboidal simple cyst-like lining to a columnar cell lining resembling normal proximal tubule, distal tubule or collecting duct. Some cysts may have an exuberant lining with enlarged clear cells, eosinophilic cells, vacuolated cells or foamy cells. Tubular ectasia may be seen in nonscarred cortex that may represent cysts in evolution (Figs. 14B, C). Calcium oxalate crystals or calcium phosphate deposits may be encountered in the interstitium or in cyst epithelium (Figs. 13B, C). Renal neoplasms may also be seen as they develop in up to 10% of patients with acquired cystic kidney disease.[64–67]

The exuberant cyst cell lining in acquired cystic kidney disease may be "atypical" with large nuclei and prominent nucleoli or show cell stratification or papillary formations, cytologic alterations that have been shown to correlate with some of the RCC types encountered in end-stage kidneys (Fig. 14D).[46,47] As some end-stage kidney-associated RCCs and some sporadic RCCs are cystic, when a cyst with an exuberant cell lining is encountered on a medical renal biopsy this could represent a benign, although possibly neoplastic cyst, or be part of cystic RCC if solid areas are present elsewhere. Ultimately imaging studies will be the final determinate.

The most common genetic kidney disease is autosomal dominant polycystic kidney disease with an incidence of 1:500 to 1000.[83–85] In autosomal dominant polycystic

TABLE 7. Cystic Kidney Disease and Renal Neoplastic Diathesis

Cystic Disease	Mutated Gene/ Protein	Cancer Risk	Tumor Types	Cyst Lining
von Hippel-Lindau disease	*VHL*/ pVHL	60% pts	Clear cell	Clear cells
Tuberous sclerosis complex	*TCS1*/ hamartin *TCS2*/ tuberin	2%-3% pts	Diverse RCCs AML and epAML	Large eosinophilic cells
ESRD +/− acquired cystic kidney disease	Diverse mutations	5%-10% pts	ACKD-assoc. RCC and other RCC types	Flat, cuboidal, columnar, stratified, papillary
Chronic lithium therapy	None identified	Not known	Oncocytoma, Papillary RCC, Clear cell RCC	Cuboidal

AKCD indicates acquired cystic kidney disease; AML, angiomyolipoma; epAML, epithelioid angiomyolipoma; ESRD, end stage renal disease; RCC, renal cell carcinoma.

kidney disease, like acquired cystic kidney disease, cysts form in the cortex and medulla. The cysts in autosomal dominant polycystic kidney disease, in contrast to acquired cystic kidney disease, initially form in normal appearing cortex (Fig. 15A). Cysts arise from all segments of the nephron, including Bowman's capsule, and from collecting ducts. Bowman's capsule involvement is particularly common in children and enters into the differential of a glomerulocystic kidney.[3]

The cysts in autosomal dominant polycystic kidney disease may have a flattened to low cuboidal cell lining similar to simple cysts and cysts in acquired cystic kidney disease (Figs. 15A–C). Cysts with exuberant cell proliferation of acquired cystic kidney disease do not occur. However, cysts with focal papillary tufts composed of a uniform low cuboidal epithelium with small uniform nuclei that lack atypia or mitotic activity occur and appear unique to autosomal dominant polycystic kidney disease. They have been reported in up to 25% of nephrectomy specimens (Fig. 15D). These usually involve large cysts and are rarely encountered in a renal biopsy. Oxalate crystals are usually not present in autosomal dominant polycystic kidney disease, but focal calcification may be seen. The clinical features of a positive family history for autosomal dominant polycystic kidney disease or markedly enlarged cystic kidneys support the diagnosis of autosomal dominant polycystic kidney disease. However, 15% to 25% of cases represent new mutations so a family history may be lacking. Infrequent small cysts, often clustered because they affect a single nephron, are present in early stages of the disease so renal enlargement may not be present. Although, the presence of multiple bilateral cysts in patient over the age of 40 may indicate autosomal dominant polycystic kidney disease, multiple simple cysts, and acquired cystic kidney disease must also be considered. The location of the cysts can help as simple cysts do not form in the medulla. The absence of chronic kidney disease argues against acquired cystic kidney disease.

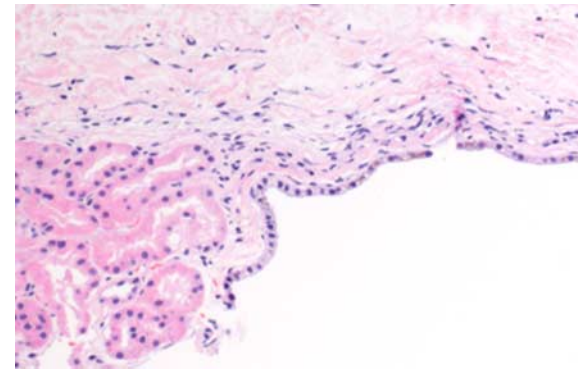

FIGURE 13. This renal biopsy from a 68-year old contains a subcapsular simple cyst. It has a low cuboidal cell lining. His kidneys are normal in size. His creatinine is normal and there is no cortical scarring.

Lithium-associated cysts have been reported in 63% of medical renal biopsies in patients on long-term lithium therapy (average13.6 y).[54,55] They form due to an anti-apoptotic effect of lithium. The cysts appear before onset of lithium-associated chronic kidney disease which may develop in up to 15% of patients. The cysts involve cortex and medulla and are usually small, 1 to 3 mm on imaging studies. The cyst cell lining consists of a uniform appearing low cuboidal epithelium with cytoplasmic clearing resembling collecting ducts (Figs. 16A, B). The cysts have a distal tubule/collecting duct immunophenotype based upon epithelial membrane antigen and lectin staining. The cysts may show pericystic fibrosis and most frequently occur in zones of tubulointerstitial scarring. The key microscopic findings of the four most common renal cysts are compared in Table 9.

Many other types of cysts may rarely be encountered in a medical renal biopsy. For instance, occasionally a patient with a history of autosomal recessive polycystic kidney disease, renal dysplasia, von Hippel-Lindau disease or tuberous sclerosis complex may be biopsied. The cysts in children with mild forms of autosomal recessive polycystic kidney disease will typically have primarily medullary cysts with few or no cortical cysts.[3] The cysts may be rounded in contour and may be associated with interstitial fibrosis resembling autosomal dominant polycystic kidney disease. The cysts in metanephric dysgenesis of a dysplastic kidney may have a diverse appearance including glomerular cysts, cystic immature ducts, and large cysts with pericystic

TABLE 8. Bosniak Type IIF, II, and IV cysts: Most Common Examples

Benign	Localized cystic kidney disease
	Pyelocalyceal diverticulum
	Abscess
	Mixed epithelial and stromal family of tumors
	Angiomyolipoma with epithelial cyst(s)
Malignant	Multilocular cystic renal cell carcinoma of low malignant potential
	Clear cell papillary renal cell carcinoma
	Tubulocystic renal cell carcinoma
	Von Hippel-Lindau disease-associated renal cell carcinoma
	Eosinophilic cystic renal cell carcinoma (Tuberous sclerosis complex-associated
	Diverse other renal cell carcinomas with focal cysts or cystic necrosis
	Cystic synovial sarcoma

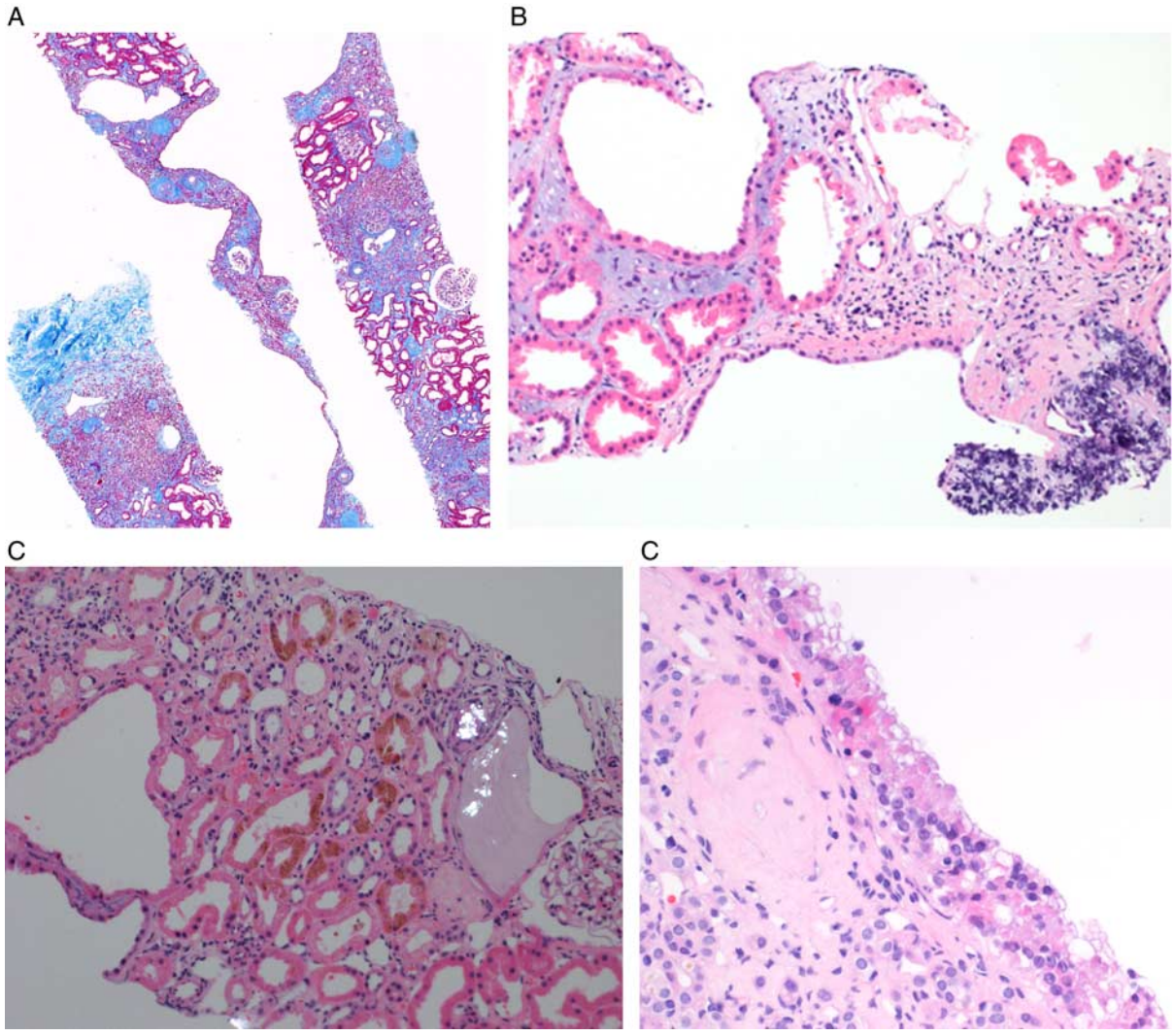

FIGURE 14. A, This example of advanced acquired cystic kidney disease shows several cysts in the midst of severe tubulointerstitial scarring. The cysts in the middle of the core are separated by a slender strip of attenuated cortex. B, This example of acquired cystic kidney disease shows a cyst lined by low cuboidal epithelium and a cyst lined by eosinophilic epithelium. Focal calcification is also present. C, This example of acquired cystic kidney disease shows multiple cysts with varying cyst linings. Birefringent oxalate crystals and hemosiderin containing tubules are also present. D, This example of acquired cystic kidney disease contains a cyst, likely neoplastic, lined by enlarged pseudostratified cells with focal vacuolization. This could be precursor of, or a cystic portion of acquired cystic kidney disease–associated renal cell carcinoma. Imaging of the kidney is warranted.

fibrosis.[3] Lower urinary tract abnormalities will usually be present and extraurinary tract malformations may also be present. The cysts in von Hippel-Lindau disease are invariably lined by clear cells while the cysts of tuberous sclerosis complex typically are lined by large densely eosinophilic cells.[68–73] Unfortunately, many renal cysts will remain unclassified because of overlapping histology between different diseases and incomplete clinical information as previously noted.

INCIDENTAL DETECTION OF A NEOPLASM ON A MEDICAL RENAL BIOPSY

The incidental detection of a renal mass in patients with abdominal imaging for a nonrenal indication is common, occurring in 14% to 40% of patients having x-ray computer tomography.[30–34] The most common mass is a benign cyst classified according to cyst complexity using the Bosniak Renal Cyst Classification as previously discussed. Solid lesions are usually neoplasms, most commonly a RCC, but are difficult to definitively classify by imaging study alone. For instance, RCCs of the various types cannot be distinguished from one another, nor distinguished from a benign oncocytoma or a myoid predominant (fat poor) angiomyolipoma. The incidental detection of a small RCC on abdominal imaging accounts for the increased incidence of RCCs observed over the past decade. This is important because an incidentally detected RCC has a much better prognosis than a symptomatic RCC.[30]

The incidental detection of a neoplasm in a medical renal biopsy also occurs, albeit infrequently, in 0.2% to 0.5% of biopsies (Table 10). The only report of incidental

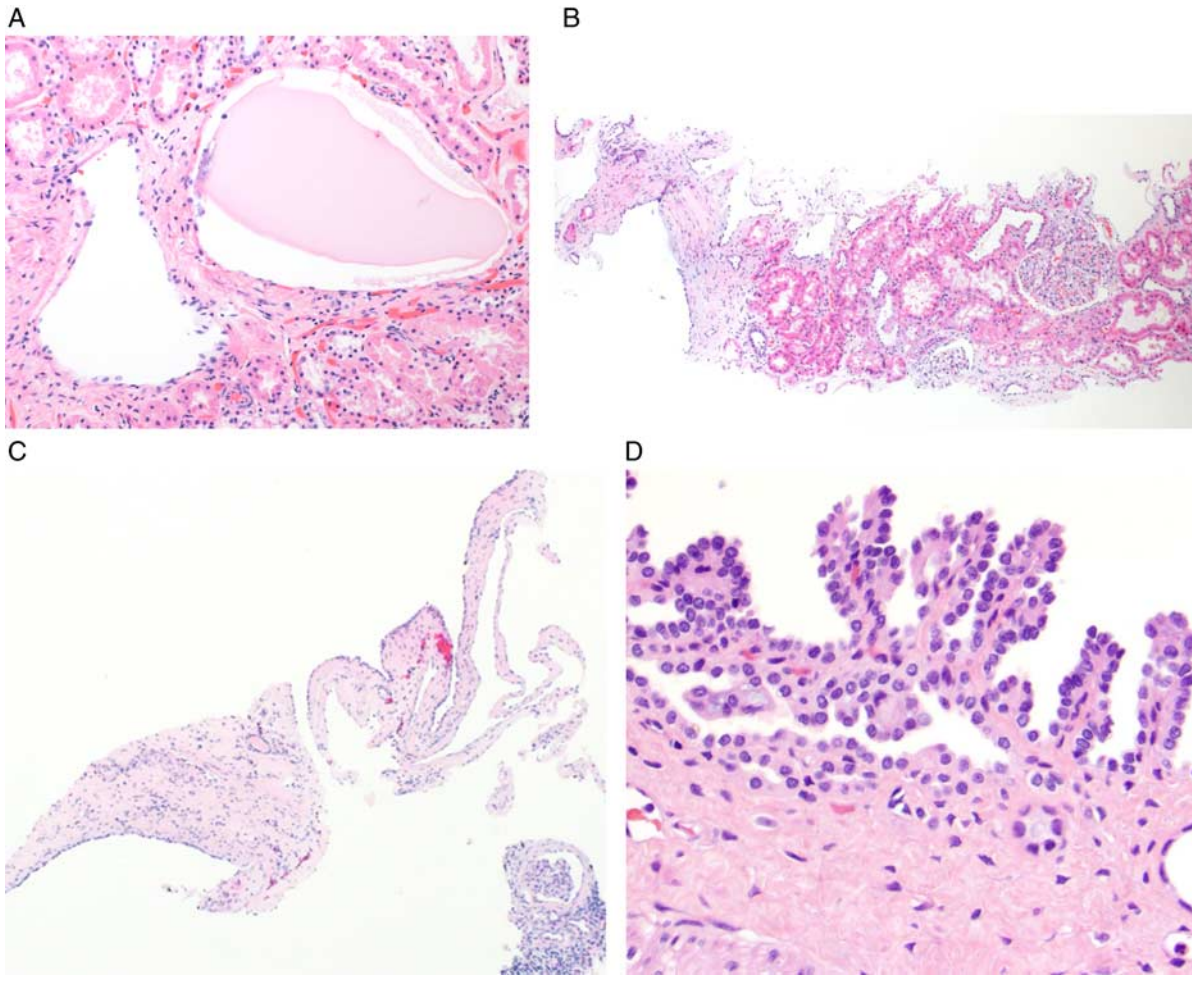

FIGURE 15. A, This example of early stage autosomal dominant polycystic kidney disease shows 2 small cysts. One contains proteinaceous fluid and focal calcification. Most of the kidney was normal. B, This example of autosomal dominant polycystic kidney disease show large cysts with pericystic fibrosis, small cysts, and a couple of ectatic tubules possibly destined to develop into cysts. C, This example of autosomal dominant polycystic kidney disease showed advanced chronicity with most of the core consisting of large cysts with extensive pericystic fibrosis. D, This example of autosomal dominant polycystic kidney disease shows a cyst with the characteristic cytologically bland small papillary tufts that are observed in 25% of nephrectomy specimens.

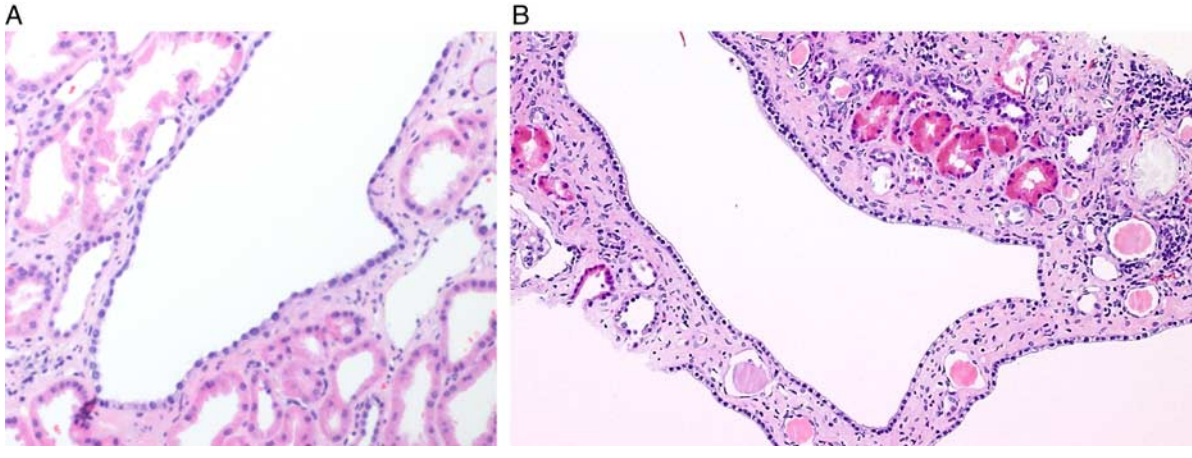

FIGURE 16. A, This example of a lithium-associated cyst demonstrates its characteristic low cuboidal collecting duct type cell lining. There was little tubulointerstitial scarring. B, This example of lithium cystic disease showed several cysts with intervening tubulointerstitial scarring.

TABLE 9. Most Common Kidney Cysts: Comparison of Histological Features

Histology	Simple Cysts	ADPKD	ACKD	Lithium
Flattened cells	+	+	+	−
Cuboidal cells	−	+	+	+
Tufts/papillae	−	+	+	−
Calcium oxalate	−	−	+	−
Cell stratification	−	−	+	−
Tumors	−	−	+	+

ACKD indicates acquired cystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease.

neoplasms on a medical renal biopsy identified 25 RCCs in a review of 11,880 cases (0.2%)[86]; 22 were classified as papillary RCC. However, since that publication many other types of RCCs have been defined, therefore, some might be classified differently today. Most RCCs encountered in biopsies are from adults over the age of 50 with chronic kidney disease possibly because chronic kidney disease and renal neoplasms have risk factors in common such as smoking, hypertension, obesity, and diabetes mellitus.[87]

A needle biopsy of a clinically detected renal mass has excellent diagnostic accuracy in distinguishing a benign from a malignant tumor (>90%), not surprising as RCCs account for ~80% of solid lesions.[31,88,89] This accuracy, however, does not necessarily translate to the incidental detection of a renal tumor in a medical renal biopsy. As a mass was not targeted by a medical renal biopsy only a small fragment of tumor may be present with most of the specimen represented by non-neoplastic kidney. In addition, the tumor may be limited to the tissue for immunofluorescence or electron microscopy comprising morphologic detail.

A small tumor fragment in a medical renal biopsy may represent a clinically insignificant tumor or represent the edge of a large clinically significant tumor with tumor size is the most important determinate. Unfortunately, tumor size cannot be established by biopsy and size information is rarely available as ultrasound used for medical renal biopsy is insensitive in mass detection. Furthermore, if a nephrologist performed the biopsy they are inexperienced in tumor recognition. Tumor size is important for several reasons. It is a major defining criteria to distinguish a papillary adenoma (<1.5 cm) from a papillary carcinoma, the most common type of tumor identified in a medical renal biopsy (Table 10).[90] Size also has prognostic importance, the smaller the mass, the greater the likelihood it is a benign tumor. Forty percent of solid masses <1 cm are benign, while tumors 4 cm or larger the percentage drops to 10%.[30,31] Finally, size correlates with likelihood of extrarenal extension and metastatic disease, and influences clinical management decisions such as active surveillance versus surgical intervention. Active surveillance is often recommended for masses 1 cm or less.[30–32]

The American College of Radiology Incidental Findings Project published management recommendations for an incidental renal mass detected on x-ray computer tomography.[30] However, there are no published guidelines for renal pathologists on the approach to an incidental neoplasm detected in a medical renal biopsy. This situation is more problematic as many renal pathologists do not sign out surgical specimens, thus, their experience in tumor diagnosis may be limited. Although a detailed discussion of the diagnostic nuances of renal tumor diagnosis is beyond the scope of this review, a broad overview with a few recommendations will be offered.

Primary renal epithelial neoplasms are the most common incidental tumor encountered in a medical renal biopsy (Table 10). However, hematopoietic neoplasms, mesenchymal tumors, and metastatic cancers also occur, and a contaminate ("floater") from another case must also be considered (Table 11). A contaminate should be considered if the tumor is not directly attached to kidney tissue. This is particularly of concern if the pathology laboratory does not have a grossing station dedicated for renal biopsies. If the tumor is attached to kidney tissue or a mass was noted on imaging, a floater can be excluded. If not, further investigation may be required.

A metastasis is the least common category of tumor in a medical renal biopsy. In a review of 20,000 consecutive cases at Arkana Laboratories 7 nonhematopoietic metastases were identified including urothelial carcinoma (0.035%). With a metastasis a history of a nonrenal primary will usually be present as a renal presentation for a carcinoma primary elsewhere is very uncommon.[91–93] Most clinically detected

TABLE 10. Incidental Neoplasms Detected in 20,000 Consecutive Renal Biopsies

Neoplasm	Number	Type
Renal cell carcinoma	31	Papillary 14, clear cell 9, other 8
Adenoma	39	Papillary 37, oncocytoma 2
Hematopoietic neoplasm	25	Lymphoma 12, CLL/WDLL 9, PTLD 2, plasma cell malignancy 1, myeloid sarcoma 1
Metastatic, nonhematopoietic	7	Urothelial 3, colon 2, breast 1 thyroid 1 melanoma 1
Benign mesenchymal	8	Angiomyolipoma 5, RMICT 2, MEST 1
Malignant mesenchymal	1	Liposarcoma
Total	111 = 0.56%	

CLL/WDLL indicates chronic lymphocytic leukemia/well differentiated lymphocytic lymphoma; MEST, mixed epithelial and stromal tumor; PTLD, posttransplant lymphoproliferative disorder; RMICT, renal medullary interstitial cell tumor.

TABLE 11. Incidental Detection of an Epithelial Neoplasm

Possibilities	Question to be Addressed
"Floater" from another case	Attached to renal tissue Biopsy grossed with other surgical cases Imaging evidence of a renal mass
Primary vs. metastatic	History of carcinoma elsewhere Recognizable type of carcinoma
Benign vs. malignant	Cytology of tumor unequivocally malignant Diagnostic features of a specific type of RCC Diagnostic features of oncocytoma, metanephric adenoma, MEST Papillary tumor, size known, appropriate histology

MEST indicates mixed epithelial and stromal family of tumor; RCC, renal cell carcinoma.

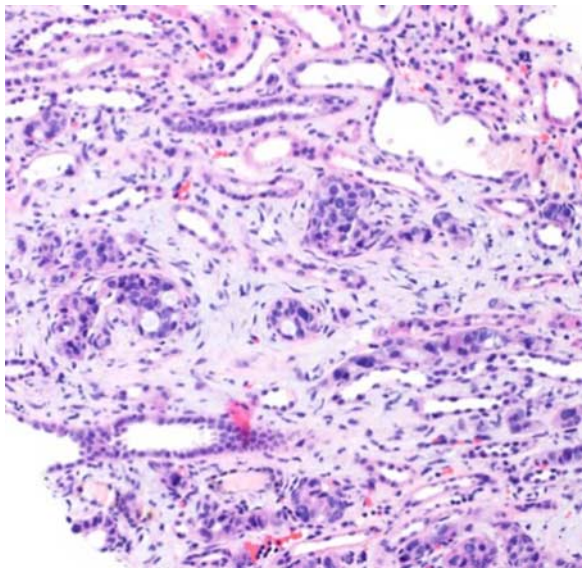

FIGURE 17. This is an example of metastatic poorly differentiated colon cancer. There is focal gland formation with mucin set in a desmoplastic stroma. The patient was known to have colon cancer but renal involvement was not suspected. The tumor is CDX2 positive.

renal metastases are solitary and unilateral, mimicking a renal primary. The time between diagnosis of the primary and detection of a renal metastasis may be as long as 5 to 10 years. Lung, ear, nose and throat, and gastrointestinal tumors are the most common solid malignancies reported but many other primary sites may be seen.[91–93] The most common RCCs and many metastatic tumors may have a distinctive histology allowing definitive diagnosis. Desmoplasia is a common finding with a metastasis but also occurs with collecting duct carcinoma and when urothelial carcinoma extends into the kidney (Fig. 17). PAX8 can be employed to implicate a renal primary as it is expressed in all RCC subtypes with a sensitivity of 95%.[94] However, other carcinomas, especially urothelial carcinoma and B-cell lymphomas may also be PAX8 positive so cautious interpretation is required.

Although most primary renal epithelial neoplasms are carcinomas, a benign epithelial neoplasm should also be considered. There are only 4 benign primary renal epithelial or mixed epithelial and stromal tumors, papillary adenoma, oncocytoma, metanephric adenoma and the mixed epithelial and stromal family of tumors.[95] In principal, excluding these 4 entities means an epithelial neoplasm is malignant by default, either primary or metastatic.

Papillary adenoma is most common of the 4 benign neoplasms and is particularly common in patients with advanced chronic kidney disease. It is defined as an unencapsulated tumor with a papillary or tubulopapillary architecture, low nuclear grade, and <1.5 cm diameter (Fig. 18A).[90] Conversely, high nuclear grade, lack of circumscription and presence of a pseudocapsule can support a malignant possibility on a medical renal biopsy. If the tumor is too small to image by magnetic resonance imaging or x-ray computer tomography scan then it will be below the 1.5 cm papillary RCC threshold. However, it must be noted that papillary architecture occurs in other types of RCC where size is not relevant to a carcinoma designation, such as clear cell papillary RCC, the MiT-TFE translocation carcinomas, oncocytic papillary RCC, and clear cell RCC with pseudopapillary growth pattern.[95,96]

Oncocytoma is the second most common benign epithelial neoplasm. It has a distinctive histology with densely eosinophilic granular cytoplasm, low nuclear grade, absent mitoses, and a distinctive CK7 staining pattern with scattered intensely positive cells (Fig. 18B). However, focal nuclear pleomorphism may be present and similar oncocytic

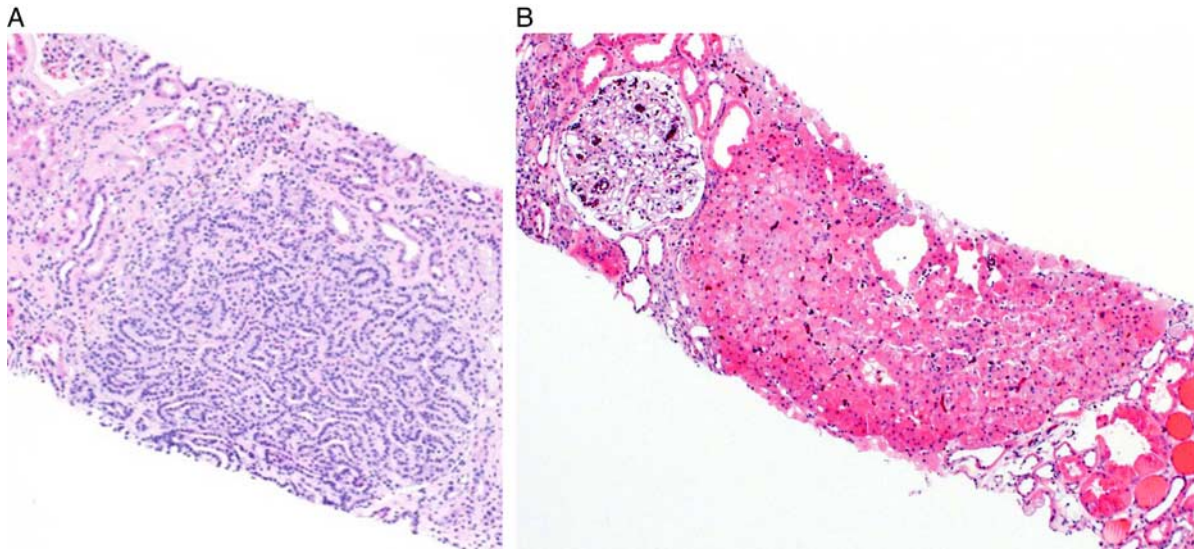

FIGURE 18. A, This is a probable papillary adenoma. It is small, well circumscribed unencapsulated with low nuclear grade. My usual approach is to call low grade papillary neoplasm, favor adenoma. B, This is an incidentally detected oncocytoma. It is low nuclear grade, well demarcated and unencapsulated. It demonstrated the typical cytokeratin 7 staining pattern with a focal intensely positive cells in a background of completely negative cells.

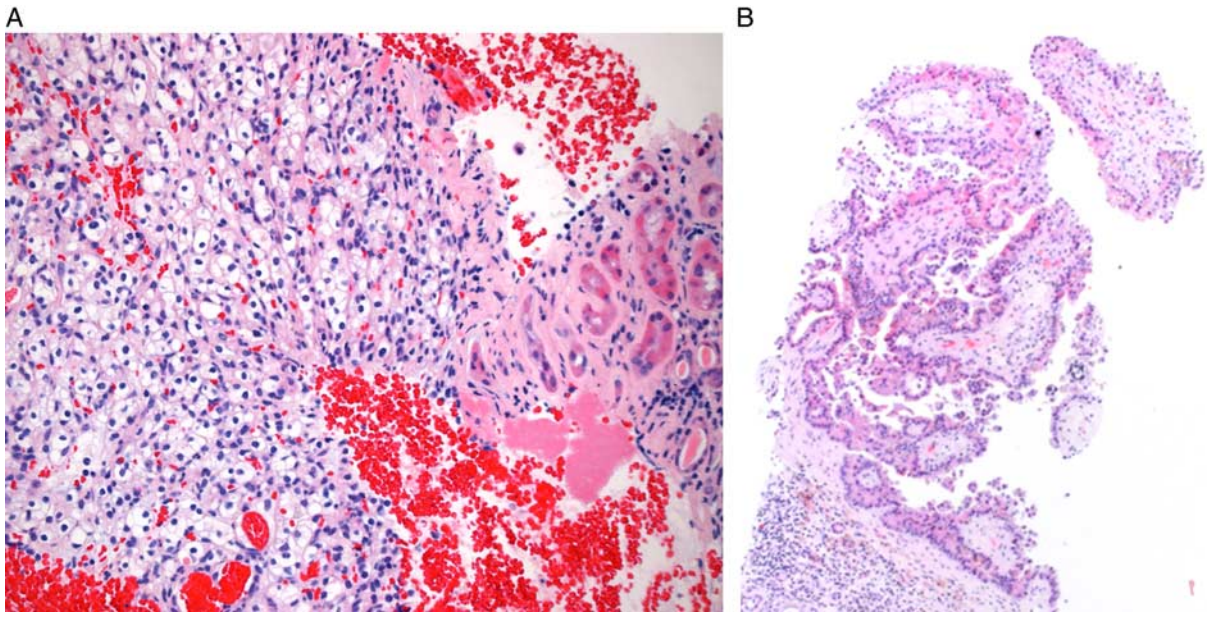

FIGURE 19. A, This is a typical clear cell renal cell carcinoma incidentially discovered on biopsy that was subsequently shown to part of a mass lesion. B, This is a probable papillary renal cell carcinoma. It is intermediate grade and has a fibrous pseudocapsule. I would diagnose as papaillary neoplasm, intermediate grade, favor papillary carcinoma and encourage imaging studies. If ultrasound performed at the time of biopsy showed a mass I would diagnose as papillary renal cell carcinoma.

appearing cells occur in the eosinophilic variant of chromophobe RCC, oncocytic papillary RCC and oncocytic angiomyolipoma.

Metanephric adenoma is a rare neoplasm with an embryonal tubulopapillary appearance that must be distinguished from a solid papillary adenoma/solid low grade papillary RCC and Wilms tumor. Immunohistochemistry is very helpful. Papillary adenoma is CK7 and AMACR positive and WT-1 and CD57 negative while metanephric adenoma stains the converse. Wilms tumor is WT-1 positive but negative for the other 3 stains.

The mixed epithelial and stromal family of tumors family of tumors includes mixed epithelial and stromal tumor and cystic nephroma. They arise deep in the kidney, often involving the medulla. Both have stromal cells that stain for estrogen and/or progesterone receptor. Cystic nephroma is diffusely cystic with a flattened to hobnail cell lining while mixed epithelial and stromal tumors has solid areas which may contain fat or smooth muscle and its epithelium can be flattened, hobnail, columnar or stratified.

Once a tumor in a medical renal biopsy is identified as a RCC the diagnosis of the subtype can be challenging. Clear cell RCC, papillary RCC and chromophobe cell RCC comprise over 90% of cases which skews the initial differential. They usually have distinctive histologic features (Figs. 19A, B). However, the World Health Organization currently recognizes 13 distinct RCC subtypes and an unclassified RCC category and there are several additional RCC subtypes widely accepted but not yet fully vetted by the World Health Organization (Table 12).[95] Furthermore, the epitheliod angiomyolipoma mimics an epithelial neoplasm. As there is considerable morphologic variation within a given RCC type and overlapping morphologic features between many RCC types, when a tiny fragment of a tumor is sampled a cautious approach to subtyping is recommended.

Immunohistochemical stains can help simplify the differential diagnosis of a RCC subtype but there are few diagnostically unique immunohistochemical profiles.[94–98] The use of immunohistochemistry for classification is driven by cell phenotype (clear cells, eosinophilic cells, distal

TABLE 12. WHO 2016 Classification of Renal Epithelial Neoplasms (Excludes Pediatric Neoplasms)

Malignant epithelial neoplasms	Benign epithelial neoplasms
Clear cell RCC	Papillary adenoma
Multilocular cystic renal neoplasm of LMP	Oncocytoma
Papillary RCC	Metanephric adenoma/ adenofibroma
Hereditary leiomyomatosis and RCC	Mixed epithelial and stromal tumor family
Chromophobe RCC	Cystic nephroma
Collecting duct RCC	Mixed epithelial and stromal tumor
Renal medullary carcinoma	Other RCCs not fully vetted by the WHO
MiT family translocation RCCs	Clear cell RCC with angioleiomyomatous stroma
Succinate dehydrogenase-deficient RCC	Thyroid carcinoma-like RCC
Mucinous tubular and spindle cell carcinoma	Carcinoma associated with neuroblastoma
Tubulocystic RCC	Oncocytic papillary RCC
Acquired cystic disease-associated RCC	ALK-translocation RCC
Clear cell papillary RCC	Renal epithelial tumor mimics
Renal cell carcinoma, unclassified	Oncocytic angiomyolipoma
	Epithelioid angiomyolipoma

LMP indicates low malignant potential; RCC, renal cell carcinoma.

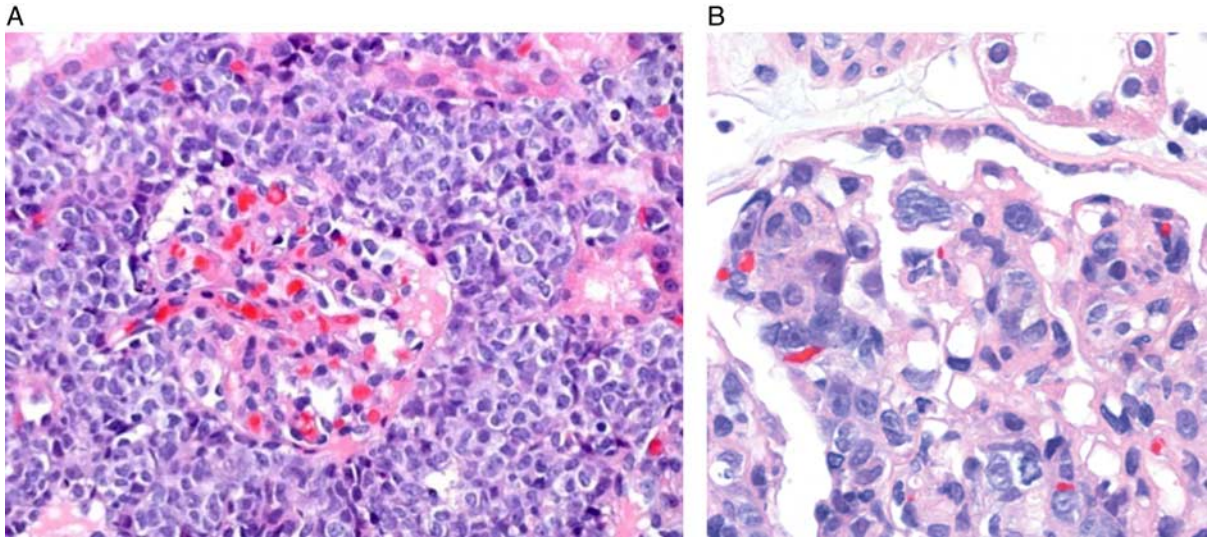

FIGURE 20. A, This high-grade lymphoma comprised 95% of the biopsy core with only a few glomeruli and tubules present to confirm renal location. The patient was biopsied for acute renal failure. The patient had bilateral enlarged kidneys but was not known to have lymphoma before biopsy. B, This intravascular B-cell lymphoma involved glomerular capillary loops and peritubular capillaries (not shown). The patient was biopsied for acute renal failure. A poorly differentiated carcinoma and melanoma must also be considered in the differential which is easily resolved by immunohistochemistry.

nephron/collecting duct-like carcinoma cells, sarcomatoid cells) or papillary architecture. In principal, molecular testing could also play a role.[96–98]

Hematopoietic neoplasms, both lymphoproliferative disorders and leukemias, are second to epithelial tumors as an incidental neoplasm (Table 10) (0.012%). They may represent a primary renal lymphoma, or a renal presentation of a lymphoma or leukemia subsequently identified elsewhere or already known.[99–102] Of the 24 cases identified in this series 13 were not known to have a hematopoietic neoplasm before medical renal biopsy. A primary renal lymphoma may seem unlikely since the kidney is devoid of native lymphoid tissue. However, many well documented cases have been reported and primary renal lymphoma represents 0.7% of extranodal lymphomas in North America.[101,102] Most are large B-cell lymphomas.

There are several patterns of renal involvement by a hematopoietic neoplasm. Rarely, it will present as a mass lesion resembling a RCC on imaging.[100] Incidental involvement on a medical renal biopsy may present as diffuse expansile interstitial infiltrates with relative preservation of tubules and glomeruli, intravascular infiltrates involving peritubular and/or glomerular capillaries or focal interstitial, capsular or perirenal fat lymphocytic infiltrates. Renal failure will usually be present in the first 2 presentations.

Diffuse interstitial involvement is usually easily recognized as a hematopoietic neoplasm. The infiltrate is discohesive and lacks architecture. It may be monotonous or markedly pleomorphic. It expands the interstitium surrounding and separating intact glomeruli and tubules (Fig. 20A). The intravascular forms fills and often distends glomerular and peritubular capillaries by large atypical cells (Fig. 20B). However, the differential includes an intravascular presentation of melanoma and high-grade carcinoma which can easily be resolved by immunohistochemistry. Although focal lymphocytic infiltrates are a typical finding in areas of scarring, they are usually ill-defined and have a polymorphous cellular composition. The presence of one or more well defined foci composed of a monotonous population of cells or the presence of capsular and perinephric fat lymphoid infiltrates should prompt consideration of a lymphoproliferative disorder (Figs. 21A–C). A simple screening approach for both obvious and suspicious cases of a lymphoproliferative disorders is to perform a CD3 and CD20 stain with 10 unstained slides cut at the same time. If there is no history of a lymphoproliferative disorders and there is a marked B-cell or T-cell predominance, or if there are obvious cytologic features of malignancy, consultation with a hematopathologist is initiated for final classification. The 10 unstained slides will usually suffice for a preliminary evaluation of the process.

The most common mesenchymal tumor in a medical renal biopsy is an angiomyolipoma (Table 10).[103–105] This is not surprising as 8% to 12% of unselected autopsy kidneys thoroughly examined have one or more angiomyolipomas.[104] An incidental angiomyolipoma may be lipid cell predominant, myoid cell predominant or triphasic with abnormal arteries (Figs. 22A, B). They are usually easily recognized although the uncommon oncocytic and epithelioid types can be diagnostically challenging. Melanocytic markers may be employed in uncertain cases. Sarcomas of renal or perirenal origin occur but are extremely rare in medical renal biopsy. Liposarcoma is the most common type but any sarcoma may arise in, or secondarily involve the kidney (Fig. 2B).

CONCLUSIONS

The kidney is affected by the most diverse collection of diseases of any organ system. This includes developmental abnormalities, neoplastic diseases, injury from the most common systemic diseases, hypertension and diabetes, and injury resulting from its filtration and tubular secretory/absorptive functions and its external environmental connection. It is the only organ in which two pathology subspecialties, renal and urologic pathology, and 2 clinical specialties, nephrology and urology, engage in diagnosis and treatment.

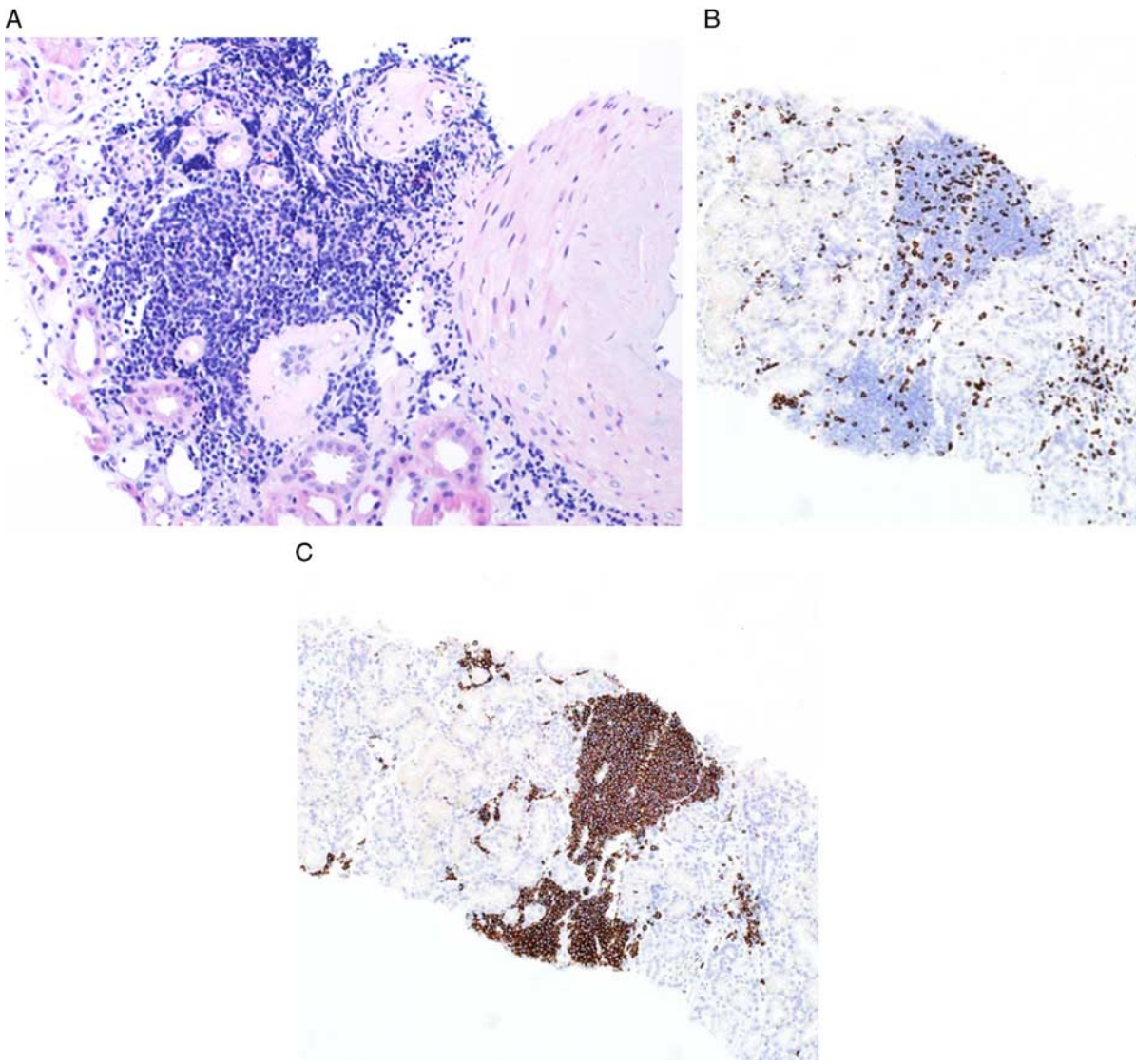

FIGURE 21. A, Chronic lymphocytic leukemia/well-differential lymphocytic lymphoma often shows multiple discrete lymphoid foci involving the cortex, medulla, renal capsule or perinephric fat in any combination. This example shows a dense monotonous lymphoid infiltrate, one of several similar cortical foci. The capsule and the perinephric fat were also involved. This was an incidental finding and not regarded as contributing significantly to the renal disease because of the small amount of tissue involved. The patient was known to have chronic lymphocytic leukemia. B, The infiltrate contained only scattered CD3 positive T cells. C, The infiltrate was predominately CD20 positive B cells.

A surgical or urologic pathologist focuses on macroscopic kidney diseases although the recent emphasis on medical renal diseases in the non-neoplastic kidney has expanded their diagnostic responsibilities. Conversely, the renal pathologist has a more microscopic focus but macroscopic renal anatomic issues and urologic diseases such as cysts and cystic kidney diseases and neoplastic diseases, periodically enter their diagnostic domain.

Renal cysts and cystic kidney diseases encompass a large number of entities. Although, their recognition or lack thereof on a medical renal biopsy rarely leads to medical treatment issues, they include genetic diseases of importance whose diagnosis may have family consoling implications. Furthermore, with advances in understanding the molecular basis for some genetic diseases, especially the most common genetic renal disease, autosomal dominant polycystic kidney disease, therapies are emerging that may delay the rate of progression making early diagnosis more important.[106]

Renal neoplasia is a rapidly expanding field with new entities appearing on a regular basis. This coupled with the often limited quantity of tumor when incidentally detected on a medical renal biopsy create great challenges for a renal pathologist. In the final analysis it is most important to simply recognize a lesion as a neoplasm on a medical renal biopsy. This may be particularly difficult if the only tumor present is in the tissue for immunofluorescence or electron microscopy. The issue of contaminate, metastasis versus renal primary, and benign versus malignant tumor must be considered but in conjunction with consultation with a hematopathologist, surgical pathologist or urologic

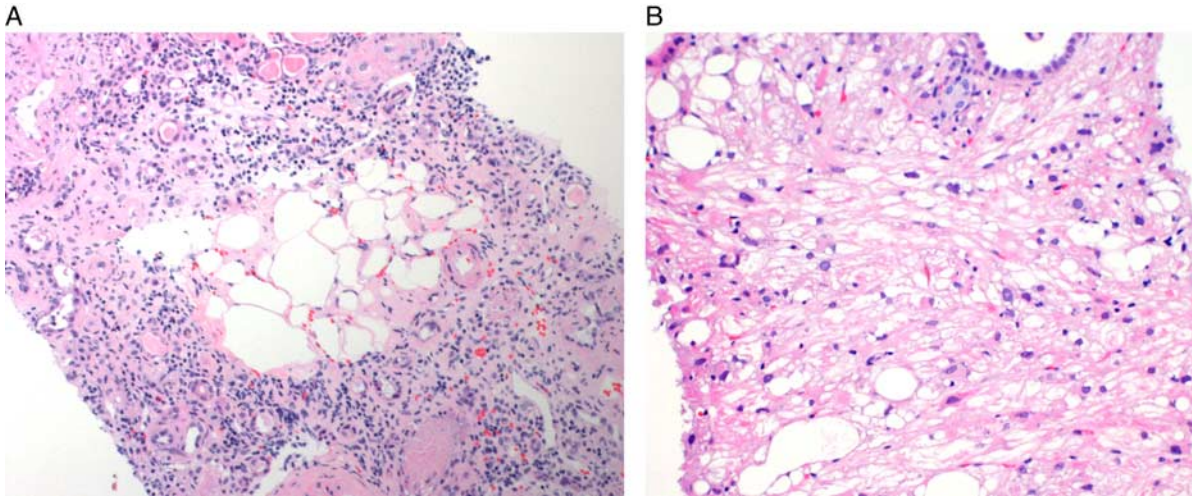

FIGURE 22. A, This is a microscopic lipid cell predominant angiomyolipoma. Between the fat cells are several inconspicuous eosinophilic myoid cells. B, This is a myoid cell predominant angiomyolipoma incidentally detected on biopsy. It contains small number of lipid cells. It was HMB-45 and MART-1 positive.

pathologist. The latter consultation is required for all cases in which a diagnosis of malignancy is entertained since Standard of Care requires a new diagnosis of cancer be reviewed by a second pathologist.

Most renal and urologic pathology fellowships have limited, or entirely lack, exposure to their kindred discipline. A significant segment of renal diseases are not, therefore, a formal part of their training programs. However, all fellows will be confronted with the full spectrum of kidney diseases in their clinical practice. This review attempts to bridge this diagnostic divide by first pointing out important anatomic features of the normal kidney, its local environment and its lymphovascular connections that may influence understanding of the findings in a medical renal biopsy. This was followed by review of some of the more common and important urologic diseases that may surface in a medical renal biopsy with general diagnostic strategies provided. It is hoped this may compliment previous publications of medical renal diseases encountered in a nephrectomy specimen. It is also hoped that this may also encourage integration of, or exposure to, urologic pathology in renal pathology fellowship programs, and vice versa, in order to optimize fellowship training.

REFERENCES

1. Bonsib SM. Renal anatomy and histology. In: Jennette JC, Olson JL, Silva FG, D'Gati V, eds. *Heptinstall's Pathology of the Kidney*, 7th ed. New York, NY: Wolters Kluwer; 2015:1–66.
2. Kambham N, Chang A. Normal kidney structure. In: Colvin RB, Chang A, Farris III, B, et al. eds. *Diagnostic Pathology Kidney Diseases*, 2nd ed. Philadelphia, PA: Elsevier; 2016.
3. Bonsib SM. Non-neoplastic disease of the kidney. In: Bostwick DG, Cheng L, eds. *Urologic Surgical Pathology*, 2nd ed. New York, NY: Mosby; 2009.
4. Bonsib SM, Pei Y. The non-neoplastic kidney in tumor nephrectomy specimens: what can it show and what is important? *Adv Anat Pathol*. 2010;17:235–250.
5. Henriksen KJ, Meehan SH, Chang A. Non-neoplastic renal diseases are often unrecognized in adult tumor nephrectomy specimens: a review of 246 cases. *Am J kid Dis*. 2007;31:575–584.
6. Mirilas P, Skandalakis JE. Surgical anatomy of the retroperitoneal spaces part II: the architecture of the retroperitoneal space. *Am Surg*. 2010;76:33–42.
7. Heller MT, Haarer KA, Thomas E, et al. Acute conditions affecting the perinephric space: imaging anatomy, pathways of disease spread, and differential diagnosis. *Emer Radiol*. 2012;19:245–254.
8. Korbet SM, Volpini KC, Whittier WL. Percutaneous renal biopsy of native kidneys: a single-center experience of 1055 biopsies. *Am J Nephrol*. 2014;39:153–162.
9. Feldmann Y, Böer K, Wolf G, et al. Complications and monitoring of percutaneous renal biopsy—a retrospective study. *Clin Nephrol*. 2017;89:260–268.
10. Kaye KW, Goldberg ME. Applied anatomy of the kidney and ureter. *Urol Clin North Am*. 1982;9:2–13.
11. Beckwith JB. National Wilms Tumor Study: an update for pathologist. *Pedatr Develop Pathol*. 1988;1:79–84.
12. Bonsib SM. The renal sinus is the principal invasive pathway: a prospective study of 100 renal cell carcinomas. *Am J Surg Pathol*. 2004;28:1594–1600.
13. Bonsib SM. Renal veins and venous extension in clear cell renal cell carcinoma. *Mod Pathol*. 2007;20:44–53.
14. Hodson CJ. The renal parenchyma and its blood supply. *Curr Prob Diagn Radiol*. 1978;7:1–32.
15. Molema G, Arid MC. Vascular heterogeneity in the kidney. *Sem Nephrol*. 2012;32:145–15.
16. Bonsib SM, Bhalodia A. Retrograde venous invasion in renal cell carcinoma: a complication of sinus vein and main renal vein invasion. *Mod Pathol*. 2011;24:1578–1585.
17. Satyapal KS. Classification of the drainage patterns of the renal veins. *J Anat*. 1995;186:329–333.
18. Sampaio FJB, Aragão AHM. Anatomic relationship between the venous arrangement and the kidney collecting system. *J Urol*. 1990;144:1089–1093.
19. Bonsib SM. Anatomy of the kidney revisited: implications for diagnosis and staging of renal cell carcinoma. In: Magi-Galluzzi C, Przybycin CG, eds. *Genitourinary Pathology*. New York, NY: Springer; 2015:280.
20. Batson OV. The function of the vertebral veins and their role in the spread of metastases. *Ann Surg*. 1940;112:138–149.
21. Nathoo N, Caris EC, Wiener JA, et al. History of the vertebral venous plexus and the significant contributions of Breschet and Batson. *Neurosurgery*. 2011;69:1007–1014.
22. Bonsib SM. Renal lymphatics, and lymphatic involvement in sinus invasive (pT3b) clear cell renal cell carcinoma: a study of 40 cases. *Mod Pathol*. 2006;19:746–753.
23. Morón FE, Szklaruk J. Learning the nodal stations in the abdomen. *Brit J Radiol*. 2007;80:841–848.

24. Parker AE. Studies on the main posterior lymph channels of the abdomen and their connections with the lymphatics of the genito-urinary system. *Am J Anat*. 1935;56:409–443.
25. Mehta V, Mudaliar K, Ghai R, et al. Renal lymph nodes for tumor staging. Appraisal of 871 nephrectomies with examination of hilar fat. *Arch Pathol Lab Med*. 2013;137:1584–1590.
26. Phan DC, McKenney JK, Cox RM, et al. Should hilar lymph nodes be expected in radical nephrectomy specimens? *Pathol Res Pract*. 2010;206:310–313.
27. Kates M, Lavery HJ, Brajtbord J, et al. Decreasing rates of lymph node dissection during radical nephrectomy for renal cell carcinoma. *Ann Surg Oncol*. 2012;19:2693–2699.
28. Bex A, Vermeeron L, Meinhardt W, et al. Intraoperative sentinel node identification and sampling in clinically node-negative renal cell carcinoma: initial experience in 20 patients. *World J Urol*. 2011;29:793–799.
29. Phillips CK, Taneja SS. The role of lymphandenectomy in the surgical management of renal cell carcinoma. *Urol Oncol*. 2004;22:214–224.
30. Herts BR, Silverman SG, Hindman NM, et al. Management of the incidental renal mass on CT: a white paper of the ACR Incidental Findings Committee. *J Am Coll Radiol*. 2017;15:264–273.
31. Leone AR, Diorio DO, Spiess, et al. Contemporary issues surrounding small renal masses: evaluation, diagnostic biopsy, nephron sparing, and novel treatment modalities. *Oncology*. 2016;30:507–514.
32. Silverman SG, Isreal GM, Tringh Q-D. Incompletely characterized incidental renal masses: emerging data support conservative management. *Radiology*. 2015;275:28–42.
33. Wood CG III, Stromberg LJ III, Harmath CB, et al. CT and MR imaging for cystic renal lesions and diseases. *RadioGraphics*. 2015;35:125–141.
34. Hindman NM. Cystic renal masses. *Abdom Radiol*. 2016;41: 1020–1034.
35. Bonsib SM. Classification of cystic kidney disease. *Arch Pathol Lab Med*. 2008;134:554–568.
36. Bisceglia M, Galliani CA, Senger C, et al. Renal cystic diseases: a review. *Adv Anat Pathol*. 2006;13:26–56.
37. Rodriquez MM. Congenital anomalies of the kidney and the urinary tract (CAKUT). *Fetal Pediatr Pathol*. 2014;33:293–320.
38. Vivante A, Kohl S, Hwang D-Y, et al. Single-gene causes of congenital anomalies of the kidney and urinary tract (CAKUT) in humans. *Pediatr Nephrol*. 2014;29:695–704.
39. Hwang D-Y, Dworschak G, Kohl S, et al. Mutation in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract. *Kidney Int*. 2014;85: 1429–1433.
40. Arts HH, Kneers NVAM. Current insights into renal ciliopathies: what can genetics teach us? *Pediatr Nephrol*. 2013;28: 863–874.
41. Chung EM, Conran RM, Schroeder JW, et al. Pediatric polycystic kidney disease and other ciliopathies: radiologic-pathologic correlation. *RadioGraphic*. 2014;34:155–178.
42. Gascue C, Katanis N, Badano JL. Cystic diseases of the kidney: ciliary dysfunction and cystogenic mechanisms. *Pediatr Nephrol*. 2011;26:1181–1195.
43. Glassberg KI, Stephens FD, Lebowitz RL, et al. The Committee on Terminology, Nomenclature, and Classification, Section of Urology, American Academy of Pediatrics. *J Urol*. 1987;138:1085–1092.
44. Deck MA, Verani R, Silva FG, et al. Histogenesis of renal cysts in end-stage renal disease (acquired cystic kidney disease): an immunohistochemical study. *Surg Pathol*. 1988;1:391–406.
45. De Oliveira Costa MZ, Bacchi CH, Franco M. Histogenesis of acquired cystic kidney disease: an immunohistochemical study. *Appl Immunohistochem Mol Morphol*. 2006;14:348–352.
46. Chen Y-B, Tickoo SK. Spectrum of preneoplastic and neoplastic cystic lesions of the kidney. *Arch Pathol Lab Med*. 2012;136:400–409.
47. Hosseini M, Antic T, Paner GP, et al. Pathologic spectrum of cysts in end-stage kidney: possible precursors to renal neoplasia. *Hum Pathol*. 2014;45:1406–1413.
48. Liu JS, Ishikawa I, Horiguchi T. Incidence of acquired renal cysts on biopsy specimens. *Nephron*. 2000;84:142–147.
49. Hughson MD, Henningar GF, McManus JF. Atypical cysts, acquired cystic kidney disease and renal cell tumors in end stage kidneys. *Lab Invest*. 1980;42:475–480.
50. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol*. 2009;20:205–2009.
51. Grantham JJ, Geiser JL, Evan AP. Cyst formation and growth in autosomal dominant polycystic kidney disease. *Kidney Int*. 1987;31:1145–1152.
52. Faraggiana T, Bernstein J, Strauss L, et al. Use of lectins in the study of histogenesis of renal cysts. *Lab Invest*. 1985;53: 575–579.
53. Bernstein J, Evan AP, Gardner KD Jr. Epithelial hyperplasia in polycystic kidney diseases: its role in pathogenesis and risk of neoplasia. *Am J Pathol*. 1987;129:92–101.
54. Markowitz GS, Radhakrishnan J, Kambham N, et al. Lithium nephrotoxicity. A progressive combined glomerular and tubulointerstitial nephropathy. *J Am Soc Nephrol*. 2000;11: 1439–1448.
55. Khan M, El-Maillakh RS. Renal microcysts and lithium. *Int J Psych Med*. 2015;50:290–298.
56. Bergman C. ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. *Pediatr Nephrol*. 2015;30:15–30.
57. Denamur E, Delezoide A-L, Alberti C, et al. Genotype-phenotype correlations in fetuses and neonates with autosomal recessive polycystic kidney disease. *Kidney Int*. 2010;77: 350–358.
58. Nakanishi K, Sweeney WE Jr, Zerres K, et al. Proximal tubular cysts in fetal human autosomal recessive polycystic kidney. *J Am Soc Nephrol*. 2000;11:760–763.
59. Baert L. Hereditary polycystic kidney disease (adult form): a microdissection study of two cases at an early stage of the disease. *Kidney Int*. 1978;13:519–525.
60. Fabris A, Anglani F, Lupo A, et al. Medullary sponge kidney: state of the art. *Nephrol Dial Transplant*. 2013;28:1111–1119.
61. Stokamn M, Lilien M, Knoers N. Nephronophthisis. GeneReviews, 1993-2018; 2016.
62. Wolf M. Nephronophthisis and related syndromes. *Curr Opin Pediatr*. 2015;27:201–211.
63. Eckdart K-U, Alper SL, Antignac C, et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—a KDIGO consensus report. *Kidney Int*. 2015;88:676–883.
64. Bonsib SM. Renal cystic diseases and renal neoplasms: a mini-review. *Clin J Am Soc Nephrol*. 2009;4:1998–2007.
65. Tickoo SK, dePeralta-Venturina MN, Harik LR, et al. Spectrum of epithelial neoplasia in end-stage renal disease. An experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic renal neoplasia. *Am J Surg Pathol*. 2006;30:14–153.
66. Bharnagar R, Alexiev BA. Renal-cell carcinoma in end-stage kidney: a clinicopathologic study with emphasis on clear-cell papillary renal-cell carcinoma and acquired cystic kidney disease-associated carcinoma. *Int J Surg Pathol*. 2012;20: 19–28.
67. Chen K, Huang HH, Aydin H, et al. Renal cell carcinoma in patients with end-stage renal disease is associated with more favorable histological features and prognosis. *Scand J Urol*. 2015;49:200–204.
68. Bernstein J. Renal cystic disease in the tuberous sclerosis complex. *Pediatr Nephrol*. 1993;7:490–495.
69. O'Callaghan FJ, Noakes MJ, Martyns CN, et al. An epidemiologic study of renal pathology in tuberous sclerosis complex. *Brit J Urol*. 2004;94:853–857.
70. Bonsib SM, Boils C, Gokden N, et al. Tuberous sclerosis complex: hamartin and tuberin expression is not indicative of mutation status. *Pathol Res Pract*. 2016;212:972–979.
71. Neumann HPH, Zbar B. Renal cysts, renal cancer and von Hippel-Lindau disease. *Kidney Int*. 1997;51:16–26.

72. Chauveau D, Duvic C, Chrétien Y, et al. Renal involvement in von-Hippel-Lindau disease. *Kidney Int*. 1996;50:944–951.
73. Solomon D, Schwartz A. Renal pathology in von Hippel-Lindau disease. *Hum Pathol*. 1988;19:1072–1079.
74. Zaidan M, Stucker F, Stengel B, et al. Increased risk of solid renal tumors in lithium-treated patients. *Kidney Int*. 2014;6:184–190.
75. Rookmaaker MB, van Gerven HA, Goldschmeding R, et al. Solid renal tumours of collecting duct origin in patients on chronic lithium therapy. *Clin Kidney J*. 2012;5:412–415.
76. Eknoyan G. A clinical view of simple and complex renal cysts. *J Am Soc Nephrol*. 2009;20:1874–1876.
77. Simms RJ, Ong ACM. How simple are "simple renal cysts"? *Nephrol Dial Transplant*. 2014;29:iv106–iv112.
78. Park H, Kim C-S. Natural 10-year history of simple renal cysts. *Korean J Urol*. 2005;56:351–356.
79. Warren KS, McFarlane J. The Bosniak classification of renal cystic masses. *Brit J Urol*. 2005;95:939.
80. Bosniak MA. The Bosniak Renal Cyst Classification: 25 years later. *Radiology*. 2012;262:781–785.
81. Muglia VF, Westphalen AC. Bosniak classification for complex renal cysts: history and critical analysis. *Radio Bras*. 2014;47:368–373.
82. Lee CT, Yang YC, Wu JD, et al. Multiple and large simple cysts are associated with prehypertension and hypertension. *Kidney Int*. 2013;3:924–930.
83. Chebib FT, Torres VE. Autosomal dominant polycystic kidney disease: core curriculum 2016. *Am J Kid Dis*. 2016;67:792–810.
84. Ready BV, Chapman AB. The spectrum of autosomal dominant polycystic kidney disease in children and adolescents. *Pediatr Nephrol*. 2017;32:31–42.
85. Rangan GK, Lopez-Vargas P, Nankivell BJ, et al. Autosomal dominant polycystic kidney disease: a path forward. *Semin Nephrol*. 2015;35:524–537.
86. Pankurst T, Howie AL, Adu D, et al. Incidental neoplasms in renal biopsies. *Nephrol Dial Transplant*. 2006;21:64–69.
87. Kabaria R, Klassen Z, Terris MK. Renal cell carcinoma: links and risks. *Int J Nephrol Renovasc Dis*. 2016;9:45–52.
88. Menogue SR, O'Brien BA, Brown AL, et al. Percutaneous core biopsy of small renal mass lesions: a diagnostic tool to better stratify patients for surgical intervention. *Brit J Urol Int*. 2012;111:E146–E151.
89. Wang R, Wolf JS Jr, Wood DP, et al. Accuracy of percutaneous core biopsy in management of small renal masses. *Urology*. 2009;73:586–590.
90. Eble JN, Moch H, Amin MD, et al. Papillary adenoma. In: Moch H, Humphrey PA, Ulbright TM, Reuter VE, eds. *WHO Classification of Tumours of the Urinary System and Male Genital Organs*. Lyon: International Agency for Research on Cancer; 2016:42–43.
91. Zhou C, Urbauer DL, Fellman BM, et al. Metastases to the kidney: a comprehensive analysis of 151 patients from a tertiary referral center. *Brit J Urol*. 2016;117:775–782.
92. Wu AJ, Mehra R, Hafez K, et al. Metastases to the kidney: a clinicopathological study of 43 cases with an emphasis on deceptive features. *Histopathology*. 2105;66:587–597.
93. Huang H, Tamboli P, Karam JA, et al. Secondary malignancies diagnosed using kidney needle core biopsies: a clinical and pathological study of 75 cases. *Hum Pathol*. 2016;52:55–60.
94. Rueter V, Argani P, Zhou M, et al. Best practices recommendations in the application of immunohistochemistry in kidney tumors: report from the International Society of Urologic Pathology Consensus Conference. *Am J Surg Pathol*. 2014;38:e35–e49.
95. Moch H, Humphrey PA, Ulbright TM, et al. *In: Srigley JR, Delahunt B, Eble JN, Reuter V, eds. WHO Classification of Tumours of the Urinary System and Male Genital Organs*. Lyon: International Agency for Research on Cancer; 2016:11–12.
96. Srigley JR, Delehunt B, Eble JN, et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *Am J Surg Pathol*. 2013;37:1469–1489.
97. Kryvenko ON, Jorda M, Argani P, et al. Diagnostic approach to eosinophilic renal neoplasms. *Arch Pathol Lab Med*. 2014;138:1531–1541.
98. Xiao X, Hu R, Deng F-M, et al. Practical applications of immunohistochemistry in the diagnosis of genitourinary tumors. *Arch Pathol Lab Med*. 2017;141:1181–1194.
99. Chen L, Richendollar B, Bunting S, et al. Lymphomas and lymphoproliferative disorders clinically presenting as renal carcinoma: a clinicopathologic study of 14 cases. *Pathology*. 2013;5:657–663.
100. Purysko AS, Westphlen AC, Remer EM, et al. Imaging manifestations of hematologic diseases with renal and perinephric involvement. *RadioGraphics*. 2016;36:1038–1054.
101. Chen X, Hu D, Fang L, et al. Primary renal lymphoma: a case report and literature review. *Oncol Lett*. 2016;12:4001–4008.
102. Sheety S, Singh AC, Babu V. Primary renal lymphoma—a case report and review of the literature. *J Clin Diagn Radiol*. 2016;10:5–7.
103. Tamboli P, Ro JY, Amin MB, et al. Benign tumors and tumor-like lesions of the adult kidney part II: benign mesenchymal and mixed neoplasms, and tumor-like lesions. *Adv Anat Pathol*. 2000;1:47–66.
104. Caliò A, Warfel KA, Eble JN. Pathological features and clinical associations of 58 small incidental angiomyolipomas of the kidney. *Hum Pathol*. 2016;58:41–46.
105. Katabathina VS, Vikram R, Nagar AM, et al. Mesenchymal tumors of the kidney in adults: imaging spectrum with radiologic-pathologic correlation. *RadioGraphics*. 2010;30:1525–1540.
106. Potts JW, Mousa SA. Recent advances in management of autosomal-dominant polycystic kidney disease. *Am J Health Syst Pharm*. 2017;74:1959–1968.