13 Kidney

Neoplasms

The kidney is primarily composed of glomeruli, tubules, stroma, and vasculature. However, unlike in some other organs, the neoplasms of the kidney do not faithfully reflect or recapitulate their cells of origin. Therefore, recognizing a lesion is not so much a systematic process as a pattern recognition. However, there are certain features to notice in evaluating any kidney mass, as they will help narrow the differential diagnosis in tough cases:

- Circumscription and/or encapsulation
- Presence of stroma within the tumor
- Vascular or capillary pattern
- Architectural pattern (solid, acinar, trabecular, tubular, papillary, pseudopapillary, cystic)
- Cellular pleomorphism (monotonous to bizarre)
- Mitotic activity
- Cytoplasm (clear to granular pink to densely eosinophilic; perinuclear halos)
- Nuclear size and contour (note the shape and whether the membrane is smooth or wrinkled)
- Nucleoli

When studying the kidney grossly, many details crucial to staging are identified (or lost) at the bench. Key prognostic factors include the following:

- Tumor extending through the kidney capsule and into the perirenal fat
- Tumor invading adrenal gland (always note whether the adrenal is even present)
- Gross tumor in the renal vein, both at the margin and in the renal pelvis (always open the renal vein)
- Tumor growing through Gerota's fascia (the very delicate membrane surrounding the perirenal fat; this is actually fairly uncommon but indicates stage IV disease)

Other helpful gross features include the following:

- Circumscription and presence of multiple lesions
- If cystic, multilocular versus unilocular, the presence of mural nodules, relationship to pelvis
- If solid, the homogeneity and the color(s)—yellow gold, mahogany brown, areas of hemorrhage, necrosis, fibrosis (gristle grey), or possible sarcomatoid foci (dense white)
- Site of origin (cortex vs. medulla or pelvis), if you can tell

Now that you have the key identifying features of your tumor, let us look at the differential diagnosis for tumors *in the adult*.

Cystic Lesions

Simple Cyst

Simple cysts are a very common finding, even at autopsy. The simple cyst is essentially a dilated tubule and will have a low cuboidal or flattened pink epithelial lining (Figure 13.1). It is usually unilocular. If multilocular, the septa dividing the cysts should be unremarkable stroma with no epithelial islands or nodules. *There should be no clear cells*.

Cystic Nephroma

Cystic nephroma is an uncommon lesion, but file it away as "one of those ectopic-ovarian-type-lesions in women." This is a multilocular cyst with a background of ovarian-type stroma

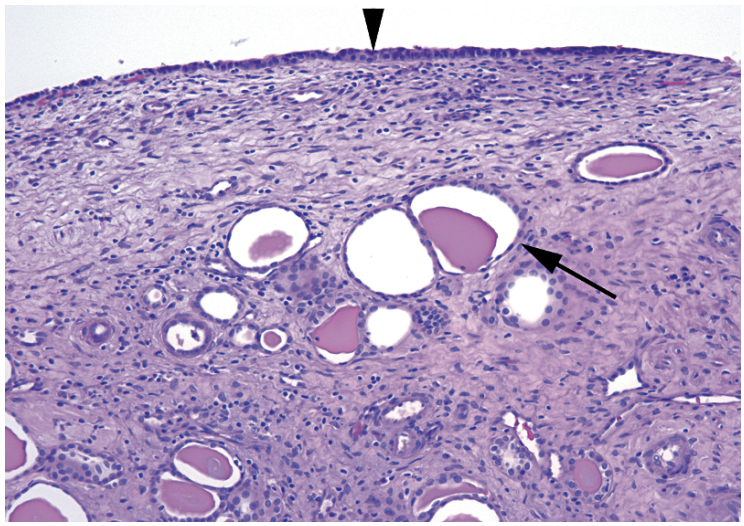

FIGURE 13.1. Simple cyst. The cyst lining (arrowhead) consists of a thin layer of cuboidal cells. Below the cyst, dilated tubules filled with proteinaceous fluid are visible (arrow).

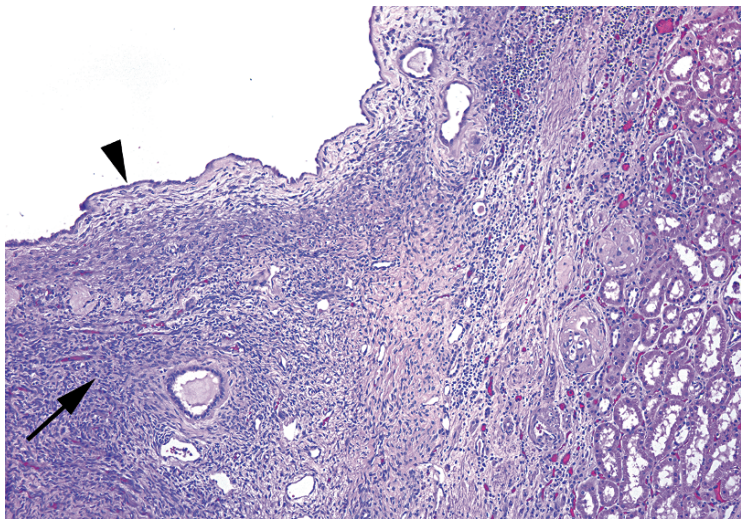

FIGURE 13.2. Cystic nephroma. Like the simple cyst, this cyst is lined with bland epithelial cells (arrowhead). However, there is adjacent spindly stroma, similar to ovarian stroma (arrow). Kidney parenchyma is seen at right.

(fairly blue, cellular, spindly, and estrogen and progesterone receptor positive; Figure 13.2). The cyst lining is cuboidal to hobnailed. *There should be no clear cells*.

Mixed Epithelial-Stromal Tumor

The mixed epithelial-stromal tumors may be cystic, but are discussed with solid lesions, below.

Renal Cell Carcinoma

Conventional (clear cell) renal cell carcinoma can present as a cyst in several ways. First, it can arise in the wall of a preexisting simple cyst. Second, it can undergo cystic degeneration of a solid tumor. Third, and most sneaky, it can occur purely as a cyst lining, usually in a multilocular cyst: this is called *multilocular cystic renal cell carcinoma*. The main indicator is *the presence of clear cells in the cyst wall* (Figure 13.3). The cyst walls may be denuded of epithelium, though, so careful sampling and hunting are essential.

Lesions With Multiple Cell Populations

Angiomyolipoma

The angiomyolipoma is, at first, a difficult lesion to recognize, because it looks like just a mishmash of normal soft tissue components. From the name, you know that it must have vessels, smooth muscle, and fat, but then so do most organs of the body. Also working against you is the fact that these lesions can have one or two components predominating, so all you see is a mass of plump spindly cells with a vessel here and there, and maybe a couple of fat cells. The key to recognizing an angiomyolipoma is knowing that you have a mass lesion and appreciating the unusual vessels that are the hallmark of this tumor.

This tumor is benign. The usual histologic features include the following:

- Large, tangled, tortuous, thick-walled, hyalinized vessels
- Smooth muscle cells (pink to clear and spindly) that seem to spin off of, or be continuous with, the vessel walls (Figure 13.4)

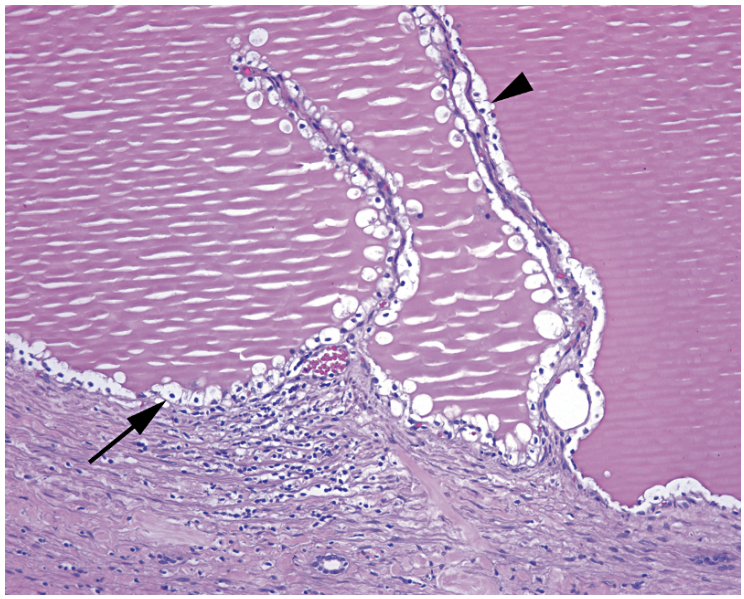

Figure 13.3. Multilocular cystic renal cell carcinoma. The cyst and fibrovascular septa (arrowhead) are lined by single clear cells with small dark nuclei (arrow); compare these cells to conventional renal cell carcinoma (see Figure 13.6).

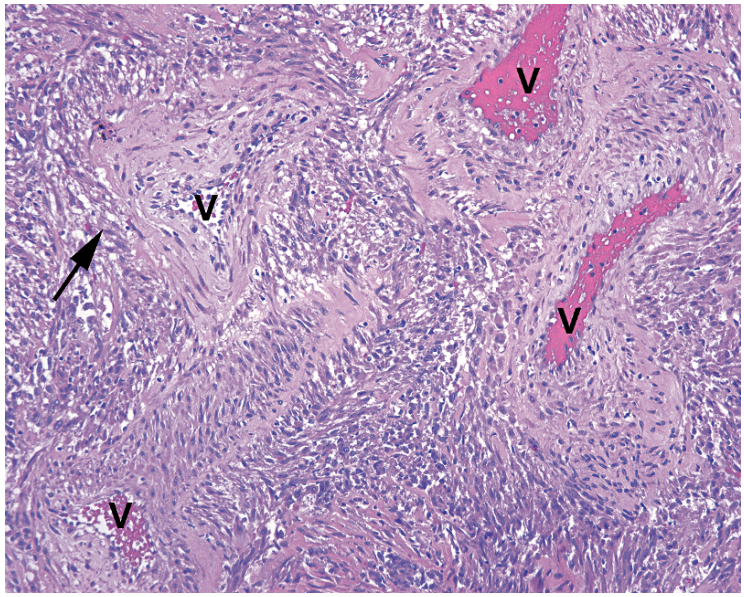

Figure 13.4. Angiomyolipoma. This example does not show the fatty component, but the prominent vessels (V) and smooth muscle components here are classic. In angiomyolipoma, the spindle cells seem to merge with, or spin off from, the thick-walled vessels (arrow).

- Mature fat cells without atypia or lipoblasts
- Pushing borders but not encapsulated
- HMB-45 and Melan-A positive (this tumor is in the perivascular epithelioid cell tumor family, all of which stain for melanoma markers)

Mixed Epithelial-Stromal Tumor

The mixed epithelial-stromal tumor, although rare, is simple in concept: it is the renal version of an adenofibroma, or a fibroadenoma, or any other benign mixture of stromal and epithelial elements. Because it can be cystic, it is also included in the differential diagnosis of cystic lesions, discussed earlier. The histologic findings include a population of cytologically benign tubules of varying shapes and sizes set in a background of bland spindled stroma, which may consist of smooth muscle, fibroblasts, or myofibroblasts. This may also be in a spectrum with cystic nephroma (discussed earlier), because it also has estrogen receptor– and progesterone receptor–positive stroma.

Solid Neoplasms

Clear Cells

The presence of clear cells in a renal tumor immediately puts renal cell carcinoma at the top of the differential. For all practical purposes, there are no benign clear cell lesions. A 3-mm clear cell focus is still a clear cell carcinoma, albeit a fairly nonthreatening one. Renal cell carcinoma is now understood to have multiple variants, but the clear cell variety is often subtitled "conventional." *Note*: Avoid the big, embarrassing, novice mistake number 1—mistaking the normal adrenal cortex for a clear cell tumor. The adrenal clear cell should have visible vacuoles that indent the nucleus, giving it a stellate outline (Figure 13.5).

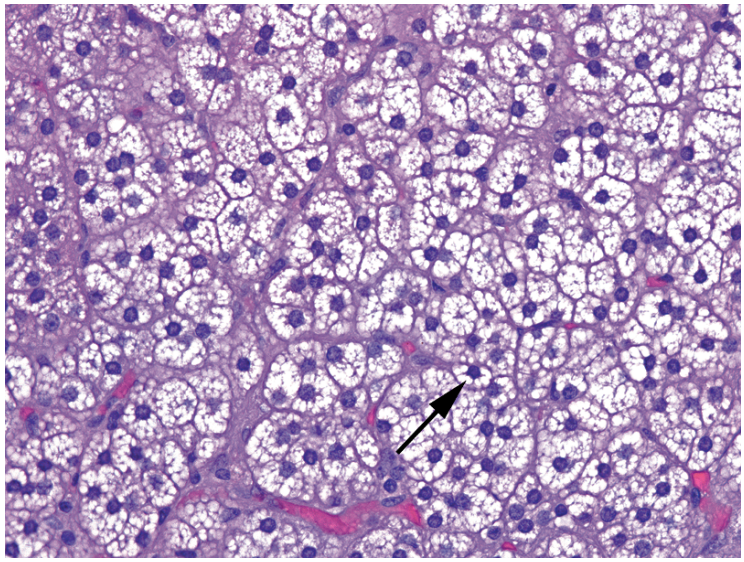

Figure 13.5. Normal adrenal cortex. Unlike clear cell carcinoma, the cells of the adrenal cortex have discrete cytoplasmic vacuoles that indent the nuclei, creating a stellate outline around the nucleus (arrow).

Renal Cell Carcinoma, Conventional or Clear Cell Type

Renal cell carcinoma is a common tumor that usually appears grossly as a granular, golden-yellowish-orange, well-circumscribed tumor, looking very much like normal adrenal tissue. It may get quite large and have areas of necrosis, hemorrhage, cystic degeneration, and fibrosis. All different-looking areas should be sampled, especially the firm solid white-to-grey areas, which could indicate sarcomatoid transformation.

Histologically, the tumor may be solid with an acinar pattern, pseudopapillary (which is an acinar pattern with centroacinar dropout), or cystic. Areas of sheeting, spindly, sarcomatoid growth will bump up the tumor to grade IV. Identifying features include the following:

- A net-like array of delicate capillaries, dividing cells into packets ("acinar" pattern)
- Clear cytoplasm, at least focally if not diffusely (Figure 13.6)
- Delicate, distinct cell membranes
- Lack of desmoplasia (although sclerosis of burned-out tumor is common)

Conventional renal cell carcinoma is graded cytologically according to *Fuhrman grade*. Low-grade tumors have clear cytoplasm, polygonal cells, and round nuclei. Higher grade tumors get pink and pleomorphic. Grade criteria, with a 10× objective (Figure 13.7), are as follows:

- Grade I: nuclei resemble lymphocytes, no nucleoli *(rarely used)*
- Grade II: nuclei still small and without nucleoli, but with open chromatin
- Grade III: easily recognizable nucleoli, larger nuclei
- Grade IV: pleomorphic and hyperchromatic nuclei with big nucleoli

Renal Cell Carcinoma, Chromophobe Variant

The chromophobe is a carcinoma that has some features of conventional renal cell carcinoma and some features of the oncocytoma. It is, overall, very pale pink under the microscope. It is not encapsulated, and it grows as a solid to papillary mass. Features include the following:

- Distinct cell membranes that give the tumor a three-dimensional texture, like alligator skin (Figure 13.8)
- Cells of varying sizes and shapes
- Pink, granular, wispy cytoplasm, often with a perinuclear clearing

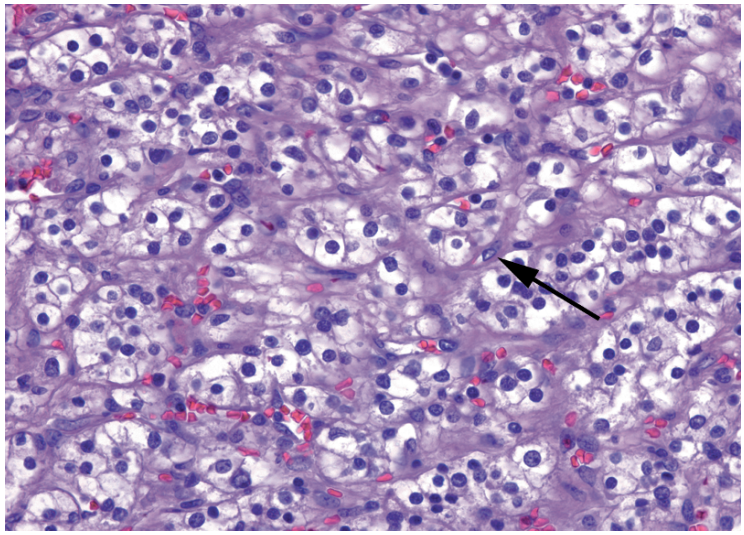

FIGURE 13.6. Clear cell renal cell carcinoma. The tumor is composed of packets of clear cells, divided by delicate fibrovascular septa (arrow). These septa are characteristic of renal cell carcinoma and are seen even in high-grade or metastatic tumors. The nuclei in this example are enlarged, but nucleoli are visible only at high power, consistent with Fuhrman grade II.

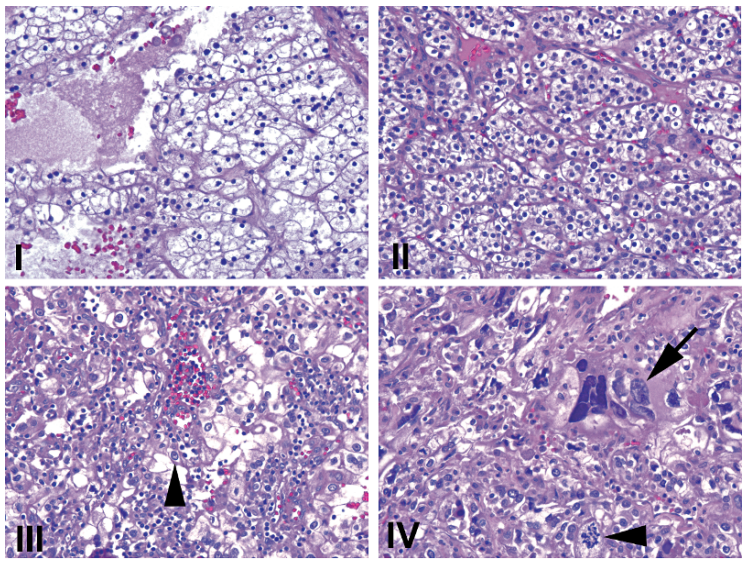

FIGURE 13.7. Fuhrman grades shown at 10×. **(I)** Nuclei are small and dense, resembling lymphocyte nuclei. **(II)** Nuclei are larger, but no nucleoli are visible at this power. **(III)** Nuclei are even larger, now with some visible nucleoli (arrowhead). **(IV)** Nuclei are frankly anaplastic (arrow) with large atypical mitoses (arrowhead). All images are taken at the same magnification.

- Nuclei that vary in size and shape and are crinkly, giving a koilocytic look (see Figure 13.8)
- Cytoplasm positive for Hale's colloidal iron
- Can transform to sarcomatoid morphology

The *eosinophilic variant of chromophobe* can look at low power like an oncocytoma, but the nuclei should still have a koilocytic flavor, unlike the very round and regular nuclei of the oncocytoma.

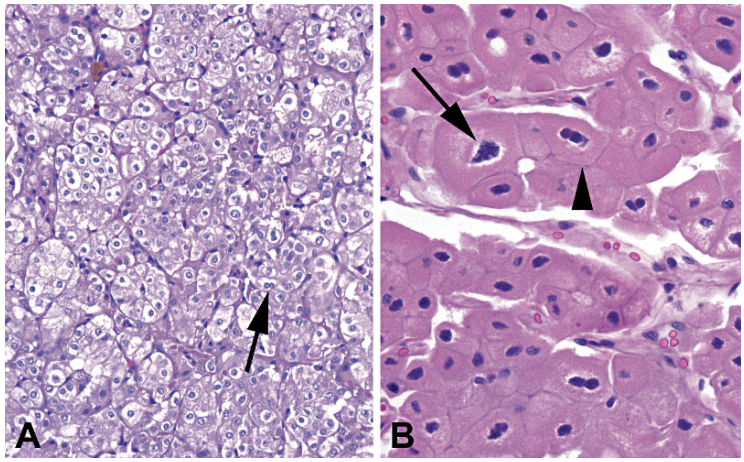

Figure 13.8. Chromophobe carcinoma. **(A)** Low-power view of a chromophobe, showing packets of cells with clear-to-pink cytoplasm, perinuclear halos, and occasional binucleate cells (arrow). The cell membranes are distinct, giving the tumor a cobblestone or alligator-skin texture. **(B)** High-power view of a chromophobe carcinoma, eosinophilic variant. Although the granular pink cytoplasm resembles an oncocytoma (see Figure 13.9), the nuclei are distinctly koilocytic, with crinkly outlines and perinuclear halos (arrow). In addition, the crisp cellular membranes are preserved (arrowhead).

Pink Cells

If the cells are not clear, your differential diagnosis includes the following:

- Chromophobe (discussed above).
- High-grade conventional renal cell carcinoma (discussed above).
- Oncocytoma: Oncocytoma is a benign tumor resembling oncocytes (or Hurthle cells) in other organs. Grossly, it is mahogany brown and well circumscribed but not encapsulated. There may be a stellate scar (a nonspecific sign of slow growth). The oncocytes are arranged in nests or cords of cells in a hypocellular stroma. The cells are round with dense pink cytoplasm and very regular, round nuclei (Figure 13.9). This regularity should strike you at low power, very different from a chromophobe. The oncocytoma is not graded. Features incompatible with this diagnosis include mitoses, papillary architecture, clear cells, and grossly identified vascular invasion.
- Papillary renal cell carcinoma: Papillary renal cell carcinoma is a cellular tumor of pink-to-blue cells (low-nuclear-grade tumors tend to be blue at low power, and high-nuclear-grade tumors tend to be pink; this seems backward) that may be arranged in papillary formations (helpful), solid sheets, or trabecular cords. The classic image is that of a fibrovascular core packed with foamy macrophages and lined by cuboidal cells with round nuclei (Figure 13.10). This image is so pathognomonic that if you find it, you are basically done. You may also see psammoma bodies, hemosiderin-laden cells, and focal clear cells.
  - Papillary adenoma: By definition, a papillary adenoma is a papillary and *non–clear cell* neoplasm of low nuclear grade and less than 5 mm in diameter.
  - Xp11: there are several translocation-defined renal cell carcinomas involving the *TFE3* gene on Xp11. They occur in young adults. Histologically, they can be summed up as clear cell tumors with papillary architecture.
- Collecting duct carcinoma: A collecting duct carcinoma is a high-grade tumor that arises in the medulla. It looks and acts much like an adenocarcinoma. The cytology is clearly malignant, there is a desmoplastic response, and it may stain for mucin and carcinoembryonic antigen. However, it is rare. Rarer still is the variant of collecting duct carcinoma found in sickle cell trait patients, the *medullary carcinoma*.

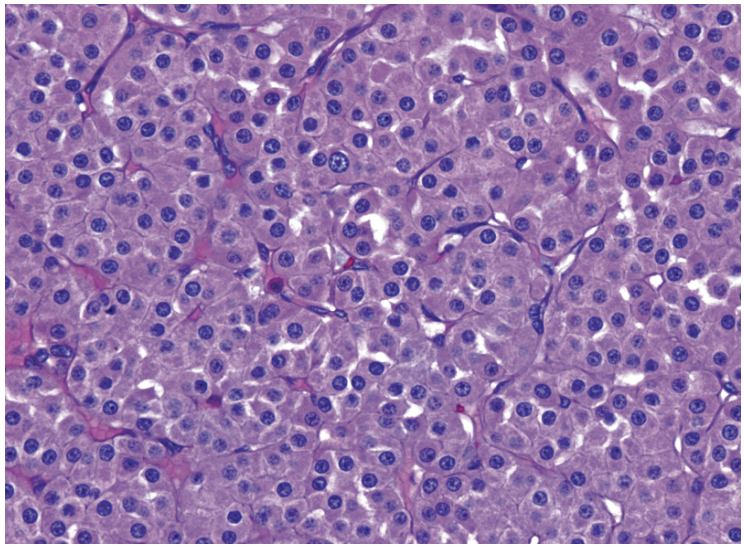

Figure 13.9. Oncocytoma. The nuclei are typically very round, uniform in size, and evenly spaced. Nucleoli may be seen, but there are no perinuclear halos. The cytoplasm is pink and granular, similar to oncocytic neoplasms elsewhere in the body.

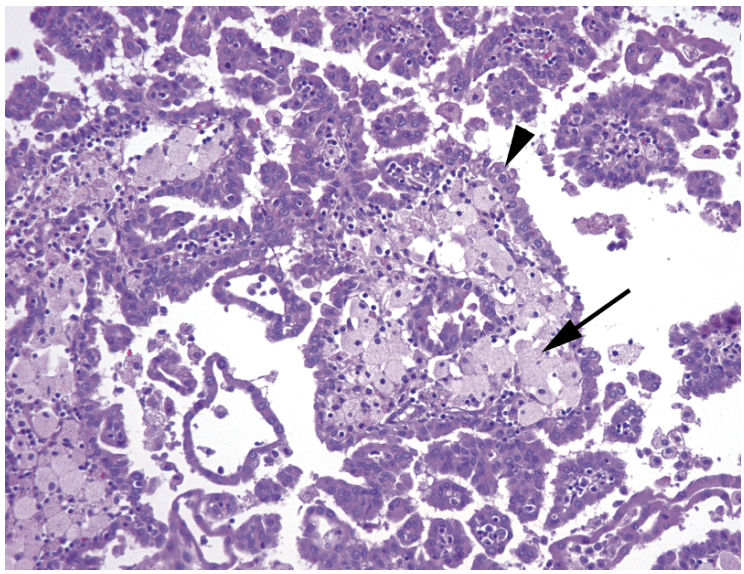

Figure 13.10. Papillary renal cell carcinoma. The tumor cells are eosinophilic, not clear, and range from cuboidal to columnar (arrowhead). This tumor may grow as solid sheets and tubules, but finding papillary structures with central cores packed with foamy histiocytes (arrow) is diagnostic. Although the tumor in this example is low grade cytologically, the cells have a relatively high nuclear/cytoplasmic ratio, and therefore this would be somewhat blue on low power.

Blue Cells

When the tumor looks blue, the differential diagnosis includes the following:

- Metanephric adenoma (blue, indigo blue, lymph node blue): Metanephric adenoma is usually a 1× diagnosis. It is a circumscribed but nonencapsulated tumor of monotonous, small, tightly packed, dense blue cells (Figure 13.11). It has little or no cytoplasm. The patterns range from tiny tubules to serpiginous gland-like structures. If this looks like a Wilms' tumor to

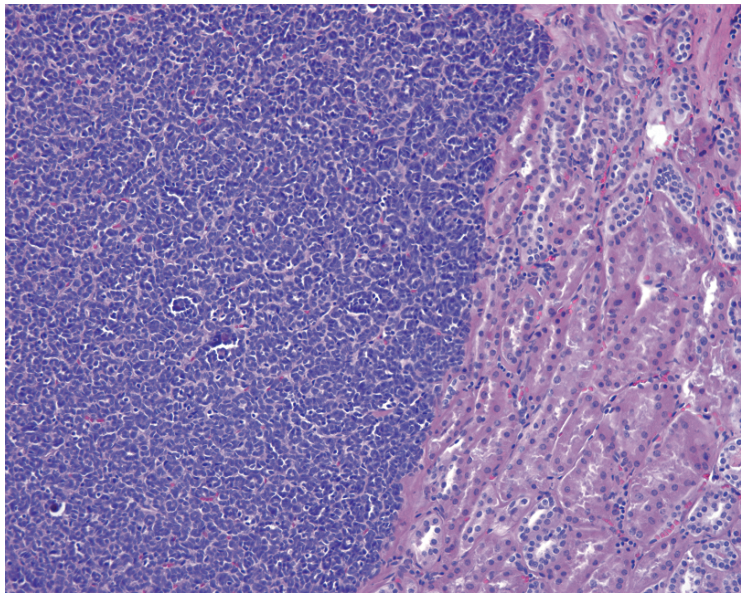

Figure 13.11. Metanephric adenoma. This benign tumor is the bluest of them all because of the very high nuclear/cytoplasmic ratio of the cells. Here you can see tiny primitive blue tubules on the left, adjacent to normal kidney on the right.

you, you are an astute observer. The metanephric adenoma may be essentially a differentiated (mature) form of a pure epithelial Wilms' tumor.

- Wilms' tumor: Wilms' tumors are unusual in adults. See the following discussion of the pediatric population.

A Brief Introduction to the Pediatric Kidney

The most common pediatric tumor is Wilms' tumor, or nephroblastoma, one of the small round blue cell tumors of childhood.

Definition of Terms

Nephrogenic rests: abnormally persistent foci of embryonal cells (small, round, and blue) that may develop into Wilms' tumor, although most do not

Blastema: sheets of undifferentiated embryonal cells in a Wilms' tumor, resembling small cell carcinoma

Anaplasia: unfavorable histology in a Wilms' tumor, defined by large, hyperchromatic nuclei and abnormal mitotic figures (tripolar)

Wilms Tumor

Wilms' tumor is defined by triphasic histology, which means you should see three components (Figure 13.12): blastema (undifferentiated, very blue), stroma (generally less cellular, more pink), and epithelium (blue like blastema but organized into tubules). One component may predominate. Histology is defined as favorable or nonfavorable, based on the presence of anaplasia. Finding foci of anaplasia requires extensive sampling and eye-grinding hunting. A Wilms' tumor may arrive at your bench post-chemotherapy. Chemotherapy changes include massive necrosis, fibrosis, histiocytic replacement, and maturation of the immature elements. One common finding is maturation to skeletal muscle cells.

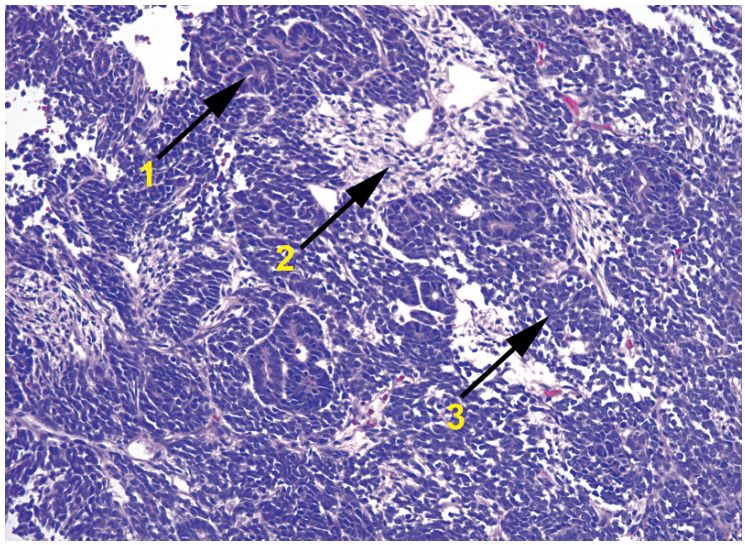

Figure 13.12. Wilms' tumor. This small round blue cell tumor classically has three components: (1) epithelium, in which the cells form primitive tubules; (2) stroma, the mesenchymal component; and (3) blastema, the most primitive and undifferentiated component. Ratios may vary by tumor.

Wilms' tumor, like renal cell carcinoma, can grossly resemble a multilocular cyst. This is called a *cystic partially differentiated nephroblastoma*. The three components are the same.

Other Pediatric Tumors

Congenital mesoblastic nephroma is a low-grade sarcoma that can resemble fibromatosis (classic type) or fibrosarcoma (cellular type). *Metanephric stromal tumor* is a spindle cell tumor that infiltrates and entraps native elements such as tubules and blood vessels. Other more aggressive tumors include *clear cell sarcoma* and *rhabdoid tumor*. Clear cell nomenclature, which is actually somewhat less than clear, is summarized in the following section.

A Note on Clear Cell Features, in General (Adults and Children)

You know about *clear cell renal cell carcinoma* (classically positive for cytokeratins and epithelial membrane antigen [EMA]). Now you also know about the *translocation tumors of the kidney*, which are clear cells on a papillary core and which arise due to translocations of the *TFE3* gene. This same gene can be translocated in the soft tissues, in which case you get *alveolar soft part sarcoma*, which may or may not be clear-cell but does resemble renal cell carcinoma because of its delicate capillary network and alveolar architecture (hence the name). This soft tissue tumor may be confused with the *clear cell sarcoma of soft tissue*, otherwise known as *melanoma of soft parts*. Like alveolar soft part sarcoma, it has an alveolar pattern and clear cells; however, it stains for the melanoma markers (S100, Melan-A, and HMB45). This tumor should not be confused with the *clear cell sarcoma of kidney*, which is totally unrelated to the clear cell sarcoma of soft tissue and is negative for most markers, including S100, cytokeratin, and EMA. However, if you are in the kidney and you have a lesion that is staining for HMB45 and Melan-A, you are most likely looking at an *angiomyolipoma*, which is a benign tumor having nothing to do with melanocytes but which does stain for the melanoma markers. Is this clear?

Medical Kidney (Non-neoplastic)

The four main compartments of the nonneoplastic kidney are the glomeruli, the tubules, the interstitium, and the vessels. The compartments are differentially affected by systemic diseases, toxins, and so forth. When evaluating the biopsy, you are looking for the following:

- In the glomeruli: the percentage of globally sclerosed glomeruli, hypercellularity (mesangial vs. endocapillary), inflammatory cells, the thickness of mesangial matrix, segmental sclerosis, hyalinosis, crescents, thrombi, and changes in the basement membrane of the capillary loops (especially by PAS and silver stains)
- In the tubules: acute and chronic inflammation in the epithelium or lumen, injury (epithelial vacuolization, necrosis, or sloughing), cellular or hyaline casts, Tamm-Horsfall protein accumulation, atrophy (dropout)
- In the interstitium: inflammation, fibrosis (especially by trichrome stain), edema
- In the arteries and arterioles: intimal thickening, hyaline deposits, emboli, thrombotic microangiopathy (fibrin thrombi, red blood cell fragments in capillary walls, fibrinoid necrosis)

This chapter does not go into great detail on these nonneoplastic entities, except to put them into the very big picture.

Acute and Chronic Damage Patterns

Nephritic Presentations

Acute injury to the glomerulus (usually immune mediated) leads to a picture of *acute glomerulonephritis* (hematuria, proteinuria, oliguria, azotemia, edema, hypertension). Histologically, the glomerulus responds with increased cellularity, which includes mesangial cells, endothelial cells, and inflammatory cells. This is a *proliferative glomerulonephritis*, and in this setting you will also see an interstitial response (edema and inflammation) and red cell casts in the tubules. Causes of this acute injury include postinfectious glomerulonephritis, IgA nephropathy, and lupus.

S*evere acute injury* causes an even more proliferative response in the form of *cellular crescents*. These are collections of epithelial and inflammatory cells in Bowman's space, hugging the glomerulus, and they are an indication of severe glomerular injury. You may also see necrosis of the glomeruli, fibrin deposition, and disruption of the basement membrane. Clinically, this appears as a *rapidly progressive glomerulonephritis* (which is the symptoms of glomerulonephritis plus acute renal failure) and causes include anti–glomerular basement membrane nephropathy (Goodpasture's syndrome), vasculitis, and anything that can cause a proliferative glomerulonephritis (see above).

Most of the above diseases are *immune-complex mediated*, so classification of the location and type of immune complex is key to subclassifying the disease. Immune complexes can be seen by electron microscopy as electron-dense areas, and their location with respect to the basement membrane is important. Immunofluorescence utilizes individual stains for IgG, IgM, IgA, and complement (C1q, C3), and their distribution also helps narrow the diagnosis. Most immune complex diseases have granular immunofluorescence staining, with the exception of anti–glomerular basement membrane disease, which has linear staining of the basement membrane.

Nephrotic Presentations

Injury that is limited to the *glomerular basement membrane* or the *podocytes* can produce a much more subtle picture. Destruction of the foot processes of the podocytes, which line the basement membrane, or disruption of the basement membrane itself, can lead to a leaky glomerulus that just shows up as proteinuria. Severe proteinuria, and the subsequent edema, hypertension, and so forth, are called the *nephrotic syndrome*. Diseases in this category include minimal change disease, focal segmental glomerulosclerosis, membranous glomerulonephritis, and membranoproliferative glomerulonephritis. Many other nonprimary renal diseases can also produce this picture, including diabetes, amyloid, lupus, drugs, and infections.

Of the four primary renal diseases listed earlier, two (minimal change and focal segmental glomerulosclerosis) are not immune complex mediated. They have little or no increase in cellularity and no immunofluorescence findings. You should see evidence of foot process damage by electron microscopy but no deposits. However, membranous and membranoproliferative are immune mediated. Both show thickened and disrupted basement membranes, granular immunofluorescence staining, and ultrastructural deposits. Membranoproliferative glomerulonephritis also has an inflammatory cellular component, so it has an added hypercellular (*hyperproliferative*) picture as well as clinical evidence of inflammation (a nephritic picture in addition to the proteinuria).

Chronic injury to the kidney produces more of a sclerotic and scarring response, as in other organs. Chronically injured glomeruli become globally sclerotic and look like whorled amorphous pink blobs in the cortex. Chronically injured tubules become flattened, sparse, and dilated, surrounded by interstitial fibrosis and chronic inflammation. When these changes are extensive, you have end-stage kidney and chronic renal failure, and it can be impossible to figure out what the original injury was.

Most of the diagnoses listed earlier are *patterns of injury*. While they can be primary renal processes, they can also represent the kidney's response to systemic diseases. Infection, drugs, and lupus are all examples of systemic diseases that can cause more than one type of kidney damage.

Diabetes and *hypertension* are common, and both are hard on the kidney. Diabetic nephropathy includes thickened basement membranes and increased mesangial matrix; it is not immune complex mediated. The hemodynamic alterations of diabetes also predispose the kidney to glomerulosclerosis, which may be nodular (the Kimmelstiel-Wilson bodies) or eventually global (end-stage kidney disease). Hypertension causes vascular changes in the kidney, including intimal fibrosis of arteries and hyaline deposits in arterioles.

Tubular diseases include acute interstitial nephritis and acute tubular necrosis. Acute interstitial nephritis is reversible damage secondary to drugs and is often associated with eosinophils. Acute tubular necrosis is acute and severe damage to the tubules causing acute renal failure. It may be caused by ischemia or a toxin.

Transplant rejection occurs in at least three forms: acute humoral, acute cellular, and chronic. Each form has specific criteria and an associated grading system. The features to look for include the following:

- In humoral rejection: glomerulitis, tubular injury, margination of neutrophils, and C4d staining in the peritubular capillaries
- In acute cellular rejection: glomerulitis, interstitial inflammation, tubulitis, and intimal arteritis
- In chronic rejection: glomerulopathy (double contours in basement membrane), mesangial matrix increase, tubular atrophy, interstitial fibrosis, intimal thickening of arteries, and hyaline thickening of arterioles

These types of rejection need to be separated from recurrence of the original disease process, preexisting donor disease (often vascular), and cyclosporine toxicity (tubular injury).