1 PEDIATRIC RENAL TUMORS

NEPHROBLASTOMA

Definition. *Nephroblastoma* is a malignant embryonal neoplasm derived from nephrogenic blastemal cells that replicates the histology of the developing kidney and often shows divergent patterns of differentiation. Nephroblastoma is also commonly known by the eponymous designation, *Wilms tumor*, after the German surgeon who was one of the first to describe this neoplasm.

General Features. Nephroblastoma is the most common pediatric renal neoplasm and affects approximately 1 in every 8,000 children (Table 1-1) (1). There are about 650 new cases every year in the United States. There is no striking gender predilection and the tumors occur with equal frequency in both kidneys. The mean ages at diagnosis are 37 and 43 months for males and females, respectively, and 98 percent of cases occur in individuals under 10 years of age, although presentation in adulthood does occur (fig. 1-1) (2–4).

The frequency of nephroblastoma around the world is stable, so environmental factors do not appear to play a major role in its development. The incidence varies among different racial groups, which suggests a genetic predisposition. Nephroblastoma is more common among African Americans than Caucasians, and least frequent among East Asians.

Approximately 10 percent of nephroblastomas develop in association with one of several well-known dysmorphic syndromes (Table 1-2) (5–9). The *WT1* gene, located on chromosome 11p13, is involved in the pathogenesis of WAGR syndrome (Wilms tumor associated with aniridia, genitourinary anomalies, and intellectual disability) and the Denys-Drash syndrome (pseudohermaphroditism, severe glomerulopathy, and Wilms tumor). *WT1* encodes a zinc finger transcription factor that is expressed in the developing kidney, gonadal sex cord stromal cells, and mesothelial cells, and plays a pivotal role in renal and gonadal development.

The WAGR syndrome is associated with germline interstitial deletions of most or all of the 11p13 band, which imparts a 30 percent chance of developing nephroblastoma, whereas the Denys-Drash syndrome is characterized by germline point mutations in the *WT1* gene, which imparts a 90 percent chance of developing nephroblastoma. Nephroblastomas in these patients typically show loss of the normal *WT1* allele, consistent with its role as a tumor suppressor gene.

A second nephroblastoma locus, which is implicated in the Beckwith-Wiedemann syndrome, maps to 11p15, where multiple imprinted candidate genes reside including *IGF2, CDKN1C (p57KIP2),* and *KCNQ1* (*KVLQT1*).

Table 1-1

FREQUENCY OF PEDIATRIC RENAL MALIGNANCIES

Neoplasm	Estimated Relative Frequency (%)
Nephroblastoma (nonanaplastic)	75-80
Nephroblastoma (anaplastic)	5-8
Congenital mesoblastic nephroma	4
Clear cell sarcoma of kidney	3-4
Rhabdoid tumor	2
Renal cell carcinoma	3-4
Miscellaneous	1-2
Neuroblastoma	
Ewing sarcoma/primitive neuroectodermal tumor (PNET)	
Synovial sarcoma	
Angiomyolipoma	
Lymphoma	
Other rare neoplasms	

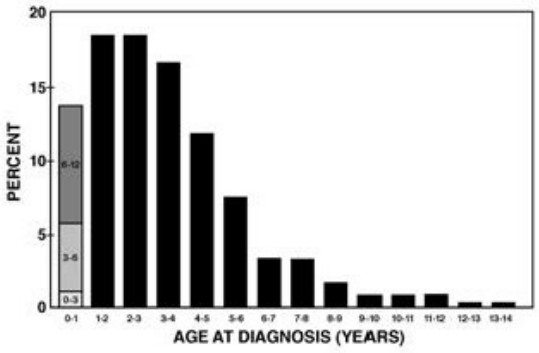


Figure 1-1

NEPHROBLASTOMA

Age distribution, based on 2,500 cases registered with the National Wilms Tumor Study Group protocols.

Table 1-2

CONDITIONS ASSOCIATED WITH NEPHROBLASTOMA

Syndromes associated with highest risk of nephroblastoma
Wilms-aniridia-genital anomaly-intellectual disability WAGR) syndrome
Beckwith-Wiedemann syndrome
Hemihypertrophy
Denys-Drash syndrome
Familial nephroblastoma
Syndromes associated with lesser risk of nephroblastoma
Frasier syndrome
Simpson-Golabi Behmel syndrome
Renal or genital malformations
Cutaneous nevi, angiomas
Trisomy 18
Klippel-Trenaunay syndrome
Neurofibromatosis
Bloom syndrome
Perlman syndrome
Sotos syndrome
Cerebral gigantism

Patients with the Beckwith-Wiedemann overgrowth syndrome have a 10 percent chance of developing nephroblastoma (Table 1-3). Familial nephroblastoma accounts for 1 percent of cases, with presumed loci responsible including 17q12-21 (FWT1) and 19q13.3-13.4 (FWT2).

Rare nephroblastomas occur in extrarenal sites (10,11). Perirenal nephroblastomas may arise by exophytic growth from the surface of the kidney or potentially by neoplastic transformation of the ureteric bud. Inguinal or perigonadal nephroblastomas are rare, and may be derived from displaced mesonephric remnants. A rare case of pure testicular triphasic nephroblastoma of germ cell origin has been described (12).

Clinical Features. Nephroblastoma most commonly presents as an abdominal mass detected by parents, often while bathing or clothing the child. Abdominal pain, hematuria, hypertension, and acute abdominal crisis secondary to traumatic rupture are less common. Rarer presentations include anemia, hypertension due to increased renin production, and polycythemia due to tumoral erythropoietin production (3).

Radiologic Features. Nephroblastoma typically manifests as a solid mass of heterogeneous appearance, distorting the renal parenchyma and collecting system. The lesion is associated with foci of calcification, but extensive punctate calcification favors neuroblastoma or Xp11 translocation renal cell carcinoma (13). Ultrasonography effectively demonstrates the cystic components of nephroblastoma. Computerized tomography (CT) is useful for identifying smaller lesions and involvement of hilar structures (fig. 1-2). Magnetic resonance imaging (MRI) of the abdomen is now preferred to abdominal CT, but CT is still the modality of choice to assess for metastatic spread to the lungs.

Tumor Spread and Staging. Nephroblastomas generally have a restricted pattern of metastasis, usually to regional lymph nodes, lungs,

Table 1-3

THREE MAIN CONGENITAL SYNDROMES ASSOCIATED WITH NEPHROBLASTOMA[a]

Syndrome	Characteristics	Chromosome Locus	Genetic Alteration	Risk of Nephroblastoma
WAGR	Aniridia, genitourinary malformations, intellectual disability, nephroblastoma	11p13	Monoallelic 11p13 involving *WT1* gene	>30%
Denys-Drash	Intersexual disorders, nephropathy, nephroblastoma	11p13	*WT1* point mutation	>90%
Beckwith-Wiedemann	Macroglossia, organomegaly, hemihypertrophy, neonatal hyperglycemia, nephroblastoma and other embryonal tumors	11p15	Duplication of paternal allele	10%

[a]Modified from Table 1 in Coppes MJ, Haber DA, Grundy PE. Genetic events in the development of Wilms' tumor. N Engl J Med 1994;331:586-90.

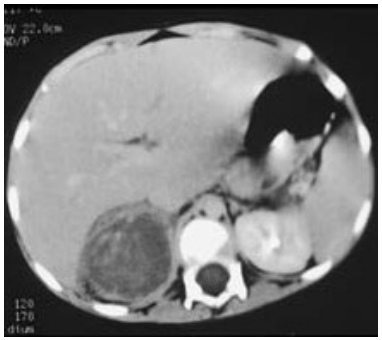


Figure 1-2

NEPHROBLASTOMA

Computerized tomography illustrates a circumscribed lesion with a heterogeneous appearance compressing the adjacent kidney. (Courtesy of Dr. D. Kelly, Birmingham, AL)

Table 1-4

REVISED SIOP WORKING CLASSIFICATION OF NEPHROBLASTOMA[a]

A. For pretreated cases
I. Low-risk tumors
Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma
II. Intermediate-risk tumors
Nephroblastoma – epithelial type
Nephroblastoma – stromal type
Nephroblastoma – mixed type
Nephroblastoma – regressive type
Nephroblastoma with focal anaplasia
III. High-risk tumors
Nephroblastoma – blastemal type
Nephroblastoma with diffuse anaplasia
B. For primary nephrectomy cases
I. Low-risk tumors
Cystic partially differentiated nephroblastoma
II. Intermediate-risk tumors
Nonanaplastic nephroblastoma and its variants
Nephroblastoma with focal anaplasia
III. High-risk tumors
Nephroblastoma with diffuse anaplasia

[a]SIOP = International Society of Pediatric Oncology.

and liver ("the three Ls"). Other metastatic sites such as bone or brain are unusual and should suggest alternative diagnoses.

Most nephroblastomas are treated using therapeutic protocols created by either the International Society of Pediatric Oncology (SIOP) or the Children's Oncology Group (COG). The SIOP protocols generally advocate preoperative therapy followed by surgical removal. In children less than 6 months of age or with completely cystic neoplasms on imaging, immediate surgical excision is recommended. Pretherapy biopsy for diagnosis is advocated only in circumstances where nephroblastoma is less likely (age >7 years, unusual clinical/radiologic features, etc.). Preresection chemotherapy promotes tumor shrinkage prior to resection, resulting in fewer intraoperative ruptures and more favorable stage distribution (more stage I to II tumors). Postoperative chemotherapy is determined by the histologic evidence of responsiveness to therapy, as indicated by post-therapy classification (Table 1-4) (14).

The COG (based on the work of the prior National Wilms Tumor Study Group) advocates

Table 1-5

STAGING OF PEDIATRIC RENAL TUMORS: CHILDREN'S ONCOLOGY GROUP (COG) AND INTERNATIONAL SOCIETY OF PEDIATRIC ONCOLOGY (SIOP)

Stage		Definition
I.	COG:	Limited to kidney and completely resected. Renal capsule is intact. Renal sinus soft tissue may be minimally infiltrated, without any involvement of the sinus vessels. The tumor may protrude into the pelvic system without infiltrating the wall of the ureter. Intrarenal vessels may be involved.
	SIOP*:	As COG but no infiltration of the renal sinus soft tissues is permitted. Limited to kidney or surrounded with fibrous pseudocapsule if outside the normal contours of the kidney. Presence of necrotic tumor or chemotherapy-induced changes in the renal sinus or soft tissue outside the kidney does not upstage the tumor in the post-therapy kidney.
*Notes:		- Fine needle aspiration or percutaneous core needle ('tru-cut') biopsy does not upstage the tumor but the size of the needle gauge should be mentioned to the pathologist. - The presence of necrotic tumor or chemotherapy-induced change in the renal sinus and/or within the perirenal fat should not be regarded as a reason for upstaging a tumor providing it is completely excised and does not reach the resection margins. - Infiltration of the adrenal gland does not upstage tumor if the external capsule of the adrenal gland is intact. - Liver: tumor might be attached to the liver capsule and this should not be regarded as infiltration of the adjacent organ; only if clear infiltration of the liver parenchyma is present, tumor should be regarded as stage III.
II.	COG and SIOP:	Tumor infiltrates beyond kidney, but is completely resected. Tumor penetration of renal capsule or infiltration of soft tissues and vessels within the renal sinus (including the intrarenal extension of the sinus). Tumor infiltrates adjacent organs or vena cava but is completely resected.
III.	COG and SIOP:	Gross or microscopic residual tumor confined to abdomen. Includes cases with any of the following: A. Involvement of specimen margins grossly or microscopically B. Tumor in abdominal lymph nodes C. Any peritoneal contamination by direct tumor growth, tumor implants, or spillage into peritoneum before or during surgery D. Residual tumor in abdomen E. Tumor removed noncontiguously (piecemeal resection)
	COG:	Tumor was surgically biopsied prior to preoperative chemotherapy (including FNA)
	SIOP:	The presence of necrotic tumor or chemotherapy-induced changes in a lymph node or at the resection margins should be regarded as stage III.
IV.	COG and SIOP:	Hematogenous or lymph node metastasis outside the abdominopelvic region.
V.	COG and SIOP:	Bilateral renal involvement at diagnosis. The tumors in each kidney should be separately substaged in these cases.

primary resection of tumors, followed by therapy that is determined by the tumor's histology and stage. This permits the diagnosis of untreated tumors and the ability to stratify them according to molecular features. While the SIOP and NWTS/COG protocols take different approaches, they have produced similar outcomes (15,16).

The most widely accepted staging systems for nephroblastomas rely on the identification of penetration of the renal capsule, involvement of renal sinus vessels, positive surgical margins, and positive regional lymph nodes. There are minor differences between the staging systems used by the SIOP and COG (Table 1-5). In general, organ-confined tumors are stage I, sinus vascular or capsular invasion denotes stage II, positive regional lymph nodes or positive surgical margins denotes stage III, and hematogenous distant metastases denotes stage IV. While bilateral nephroblastomas are designated as stage V, their prognosis is determined by the local stage of the most advanced tumor and by the presence or absence of anaplasia.

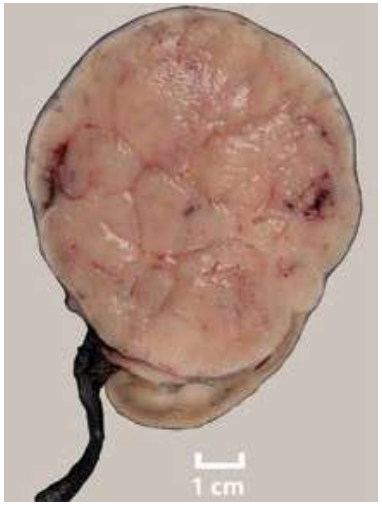


Figure 1-3

NEPHROBLASTOMA

Grossly, nephroblastomas commonly have a mucoid gray-white appearance, a sharply demarcated spherical shape, internal nodularity, and a pushing growth pattern.

Gross Findings. Most nephroblastomas are unicentric (fig. 1-3). Nevertheless, multicentric tumors in a single kidney and bilateral primary tumors are seen in 7 and 5 percent of cases, respectively (17). Multicentric nephroblastomas are associated with nephrogenic rests in almost all cases, tend to occur in younger patients, are slightly more common in females, and pose the added risk of renal failure due to obliteration of functioning nephrons by tumor or their loss by surgery (fig. 1-4).

Nephroblastomas are usually rounded, multinodular masses that are sharply demarcated from the adjacent renal parenchyma by a peritumoral fibrous pseudocapsule. The cut surface is characteristically bulging and lobulated, since the neoplasm is subdivided by prominent septa. The cut surface of untreated tumors is usually pale gray or tan, and has a soft consistency, although it may be firm and whorled if a large fraction of the lesion is composed of mature

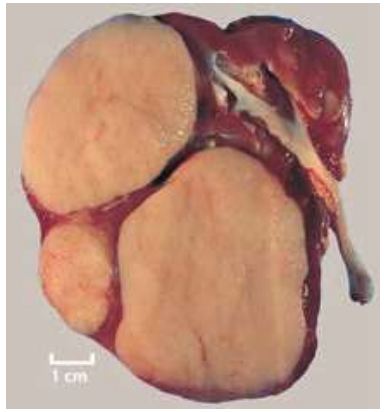


Figure 1-4

MULTICENTRIC NEPHROBLASTOMA

Three spherical nodules are separated by renal parenchyma.

stromal elements. Many tumors are friable and contain hemorrhage and necrosis, which contributes to artefactual displacement when sectioned. Cystic change may be extensive and may or may not be secondary to necrosis (see Differential Diagnosis).

Polypoid extensions of nephroblastoma into the renal pelvis and collecting systems commonly result in a botryoid gross and microscopic appearance (fig. 1-5) (17a). Tumors treated with preoperative chemotherapy usually show areas of necrosis or are completely necrotic, and may have prominent cysts.

Microscopic Findings. Nephroblastomas characteristically contain undifferentiated blastemal cells, and cells differentiating to various degrees and in different proportions toward epithelial and stromal cells (fig. 1-6). Triphasic patterns are the most characteristic, but biphasic and monophasic lesions are often observed. A *central epithelial* pattern, characterized by central tubules surrounded by blastemal cells, recapitulates the condensation of blastemal cells around the branching ureteric bud during development (fig. 1-7). While most of these

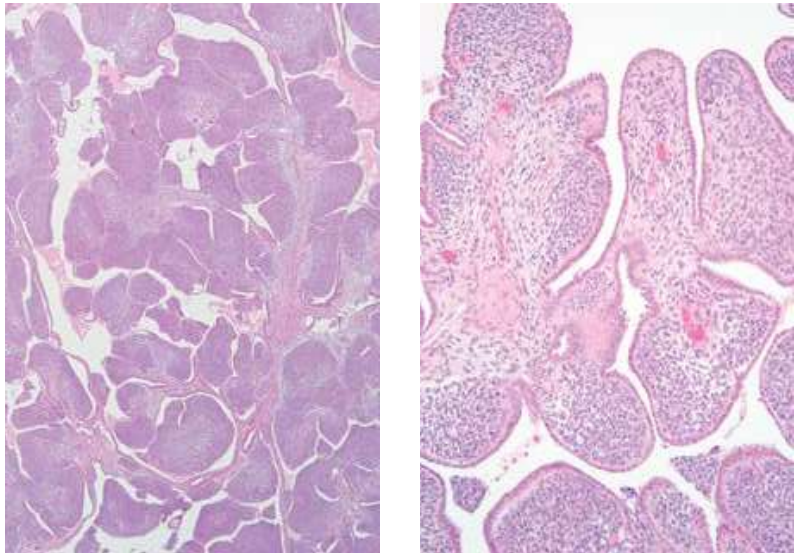


Figure 1-5

BOTRYOID NEPHROBLASTOMA

Left: This papillary neoplasm projected into the renal pelvis.

Right: The stroma consists of blastemal nodules and spindled stroma, while the lining is neoplastic primitive epithelium. In other areas, the neoplasm undermined non-neoplastic renal pelvic urothelium.

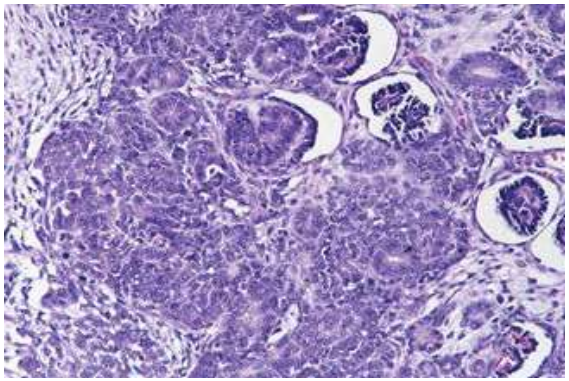


Figure 1-6

NEPHROBLASTOMA

Triphasic pattern, with blastemal, stromal, and epithelial elements consisting of tubules and primitive glomeruli.

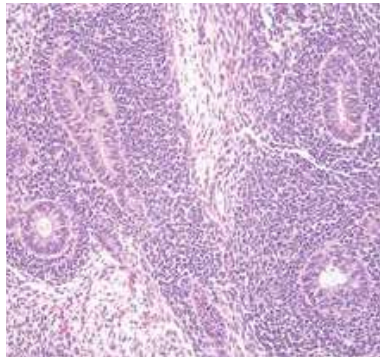


Figure 1-7

NEPHROBLASTOMA

The central epithelial pattern to the right is characterized by a central tubule surrounded by blastemal cells.

components represent stages in normal or abnormal nephrogenesis, heterologous nonrenal elements also occur.

The blastemal cells of nephroblastoma recapitulate the condensed mesenchyme that is normally present at the edge of the lobes of the developing kidney between weeks 8 and 36 of gestation. Blastemal cells are small, closely packed, mitotically active, rounded or oval cells with scant cytoplasm (fig. 1-8). The nuclei are characteristically overlapping, with evenly distributed, slightly coarse chromatin and small nucleoli (fig. 1-9). The closely packed blastemal nuclei mold to each other like those of small cell carcinoma. Poor fixation of blastemal nuclei results in prominent artefactual clearing, which combined with a prominent capillary vasculature, can mimic the morphology of clear cell sarcoma of the kidney.

Several distinctive blastemal patterns have been described. The *diffuse blastemal* pattern is characterized by a lack of cellular cohesiveness and aggressive invasion into adjacent connective tissues and vessels, contrasting with the typical circumscribed, encapsulated, "pushing" border characteristic of most nephroblastomas (fig. 1-10). Diffuse blastemal nephroblastoma frequently presents at an advanced stage and

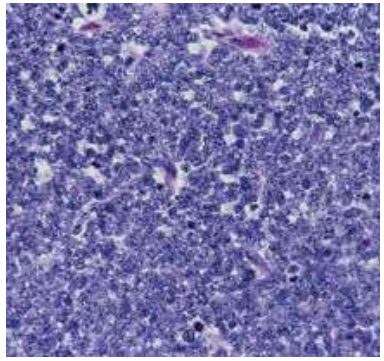


Figure 1-8

NEPHROBLASTOMA

Blastemal cells are primitive small round cells, which invite confusion with other small round blue cell tumors of childhood. The nuclei overlap and have evenly dispersed chromatin.

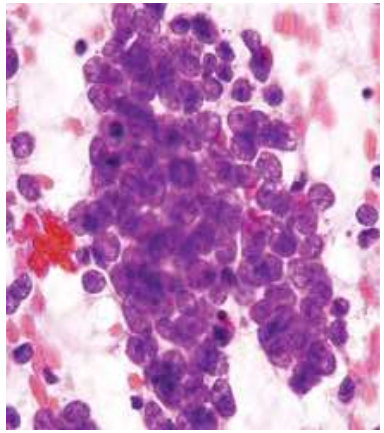


Figure 1-9

NEPHROBLASTOMA

Smear preparation demonstrates cohesive clusters of blastemal cells with evenly distributed hyperchromatic chromatin and small nucleoli.

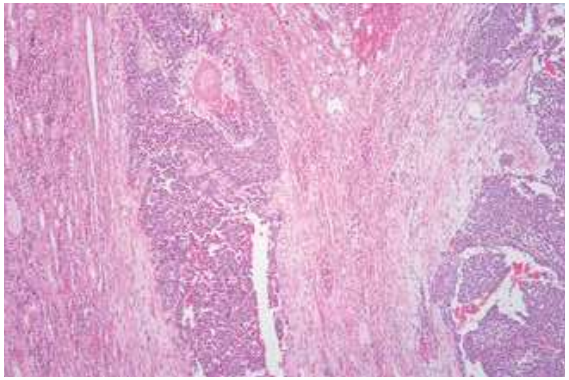


Figure 1-10

NEPHROBLASTOMA

The diffuse blastemal pattern is characteristically highly invasive, with nodules of neoplasm (likely representing vascular invasion) (left) surrounding the main neoplasm (right).

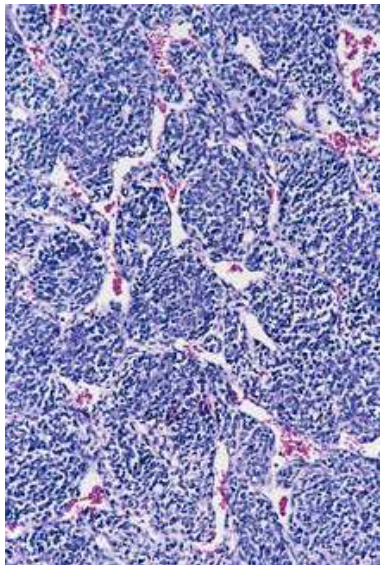


Figure 1-11

NEPHROBLASTOMA

The distinct nodular blastemal pattern is uncommonly seen in other small round tumors of childhood.

Table 1-6

SMALL ROUND CELL TUMORS OF KIDNEY

Blastemal nephroblastoma
Renal Ewing sarcoma/primitive neuroectodermal tumor
Renal neuroblastoma
Renal lymphoma
Cellular clear cell sarcoma of kidney
Rhabdoid tumor, lymphomatoid variant
Desmoplastic small round cell tumor

in extrarenal sites, and other small round blue cell tumors of childhood are in the differential diagnosis (Table 1-6).

Other blastemal patterns are more cohesive and accordingly less consistently associated with high stage, and their morphology is also more characteristic of nephroblastoma than other small round blue cell tumors. The *nodular* (fig. 1-11) and *serpentine* (fig. 1-12) *blastemal* patterns demonstrate round or undulating, sharply defined cords or nests of blastemal cells set in a loose fibromyxoid stroma. The *basaloid blastemal* pattern results when one of the two cohesive blastemal patterns is associated with a distinctive peripheral palisaded epithelial layer (fig. 1-13).

Most nephroblastomas contain an epithelial component; early tubular forms resemble primitive rosette-like structures (fig. 1-14), but most contain easily recognizable tubular or

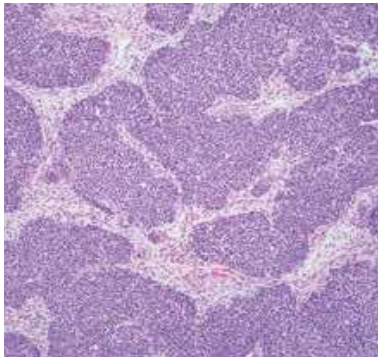


Figure 1-12

NEPHROBLASTOMA

The serpentine blastemal pattern, characterized by round or undulating, sharply delineated cords of blastemal cells in a loose fibromyxoid stroma, is highly characteristic of nephroblastoma.

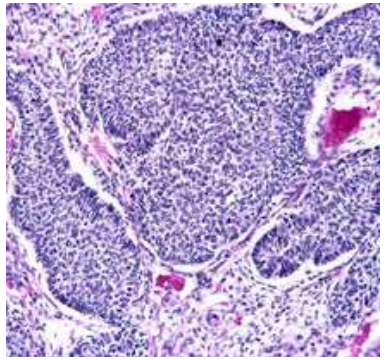


Figure 1-13

NEPHROBLASTOMA

The basaloid blastemal pattern shows a distinctive peripheral palisaded epithelial layer, reminiscent of cutaneous basal cell carcinoma.

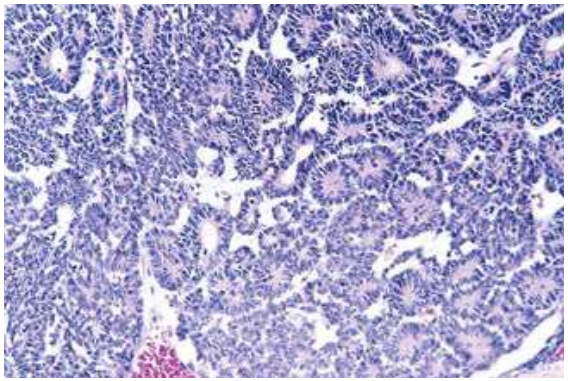


Figure 1-14

NEPHROBLASTOMA

The early primitive tubules of nephroblastoma lack lumens, and invite confusion with Homer-Wright rosettes. Areas with true tubular lumens (upper left and right) are focally present.

glomerular elements that recapitulate various stages of normal nephrogenesis. The nuclei of primitive tubules are often slightly larger than those of the adjacent blastemal cells (fig. 1-15). Heterologous epithelial differentiation most commonly consists of mucinous and squamous epithelium (Table 1-7; fig. 1-16). Pure tubular differentiated nephroblastomas are distinctive: they typically present at young age and low stage, confer an excellent prognosis, and harbor a different mutational profile than other nephroblastomas.

The most common stromal pattern consists of nondescript spindle cells in a myxoid stroma

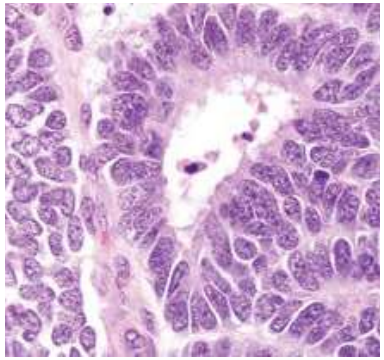


Figure 1-15

NEPHROBLASTOMA

In most favorable histology nephroblastomas like this one, the nuclei of primitive tubules (right) appear slightly larger than those of adjacent blastemal cells (left).

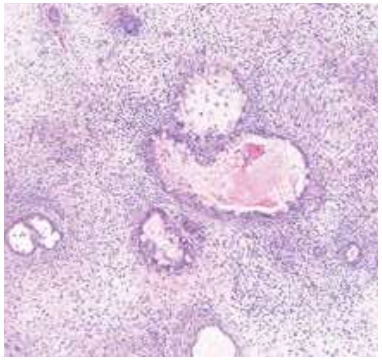


Figure 1-16

NEPHROBLASTOMA

Neoplastic glands with mucinous epithelium, including goblet cells, are surrounded by myxoid stroma.

Table 1-7

EPITHELIAL PATTERNS IN NEPHROBLASTOMA

Patterns or cells resembling nephrogenesis
Tubular
Glomeruloid
Papillary
Transitional
Heterologous cell types
Mucinous cells
Squamous cells
Neuroendocrine cells

Table 1-8

STROMAL CELLS IN NEPHROBLASTOMA

Undifferentiated stromal cells, often in a myxoid background
Fibroblasts, myofibroblasts
Smooth muscle cells
Skeletal muscle cells
Adipose cells
Cartilage
Osteoid (bone)
Neuroglial cells

resembling embryonal mesenchyme (Table 1-8). Hypocellular stromal areas are distinguished from reactive stroma by greater cellularity and more primitive nuclei (fig. 1-17). More cellular spindle cell stroma can overlap in appearance with monophasic synovial sarcoma (fig. 1-18). The stroma also frequently shows smooth muscle and fibroblastic differentiation. Skeletal muscle is the most common heterologous stromal cell type and may comprise large fields of the tumor (fig. 1-19).

Nephroblastomas with an extensive differentiated skeletal muscle component have been termed "fetal rhabdomyomatous nephroblastoma." However, this pattern lacks clinical significance and the term is thus discouraged to avoid unnecessary confusion (fig. 1-20). When polypoid projections of nephroblastoma extend into the lumen of the pelvicalyceal system, primitive skeletal muscle cells frequently condense beneath the pelvic urothelium, simulating the cambium layer of botryoid embryonal rhabdomyosarcoma. Importantly, the presence of skeletal muscle differentiation in a primary pediatric renal neoplasm is strong evidence in support of the diagnosis of nephroblastoma.

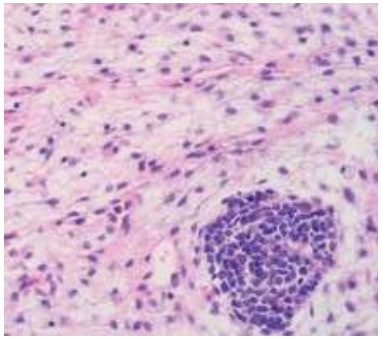


Figure 1-17

NEPHROBLASTOMA

Hypocellular stroma is distinguished from reactive stroma by greater cellularity and more primitive-appearing nuclei. A nodule of primitive blastemal cells is noted at the lower right.

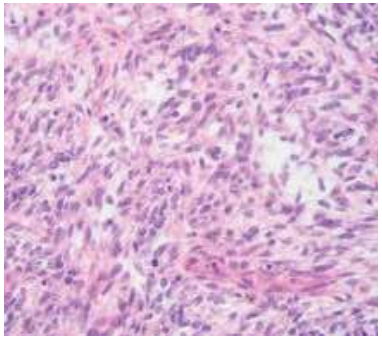


Figure 1-18

NEPHROBLASTOMA

More cellular spindle cell stroma can resemble monophasic synovial sarcoma.

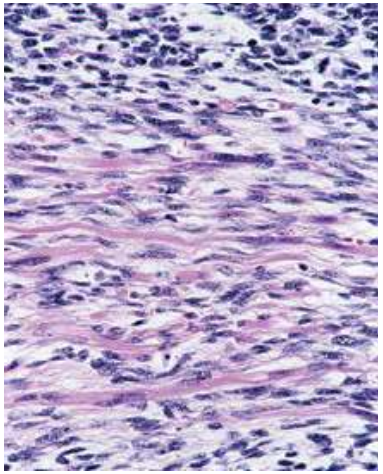


Figure 1-19

NEPHROBLASTOMA

Skeletal muscle is the most common heterologous stromal cell type in nephroblastoma.

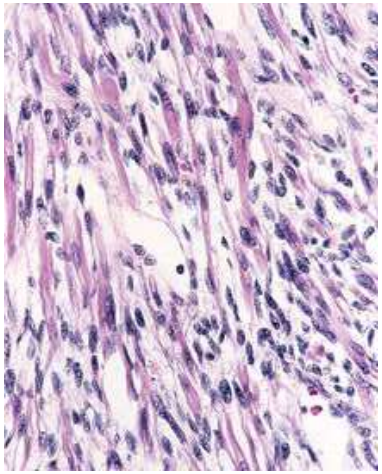


Figure 1-20

NEPHROBLASTOMA

Highly differentiated skeletal muscle in nephroblastoma can resemble fetal rhabdomyoma. This morphologic pattern has no clinical significance.

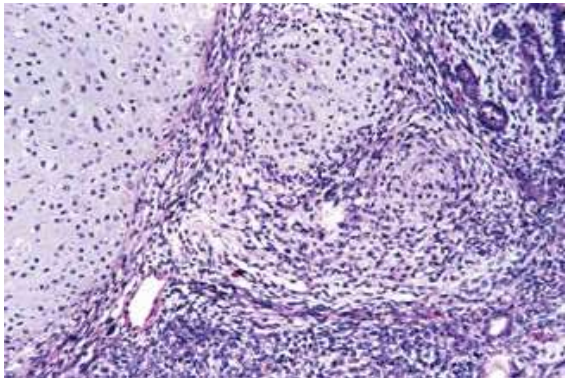


Figure 1-21

NEPHROBLASTOMA

Islands of cartilaginous differentiation (left) merge with primitive blastemal cells and tubules (right).

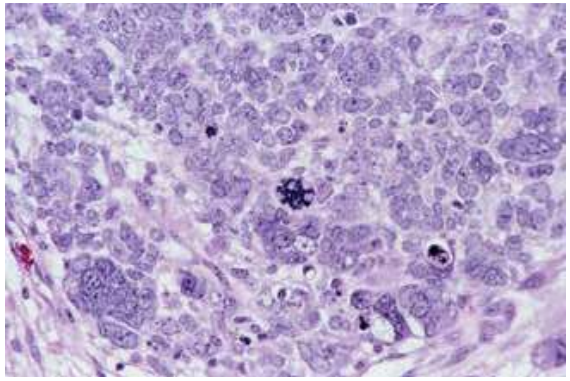


Figure 1-22

ANAPLASTIC NEPHROBLASTOMA

The multipolar mitotic figure in the center of the field is distinct from the smaller normal mitotic figures at the periphery. A markedly enlarged polypoid nucleus is present at the lower left.

Other types of heterologous stromal differentiation include adipose tissue, cartilage (fig. 1-21), bone, ganglion cells, and neuroglial tissue. Stromal components typically predominate in nephroblastomas associated with intralobar nephrogenic rests, while blastemal and epithelial components predominate in nephroblastomas associated with perilobar nephrogenic rests.

Favorable Versus Unfavorable Histology. While the different components of nephroblastoma create a wide range of morphologic appearances and a corresponding broad range of differential diagnoses, most nephroblastomas remain highly sensitive to chemotherapy and are considered to have "favorable histology." Unfavorable histology nephroblastomas are resistant to chemotherapy, and are defined morphologically by the presence of anaplasia.

Anaplasia, defined as cells with huge hyperchromatic nuclei, associated with multipolar mitotic figures (figs. 1-22, 1-23), is seen in 5 to 10 percent of nephroblastomas. The major dimensions of these nuclei are at least three times that of nonanaplastic nuclei in other areas of the specimen. Nuclear elongation alone is insufficient for anaplasia; all dimensions should

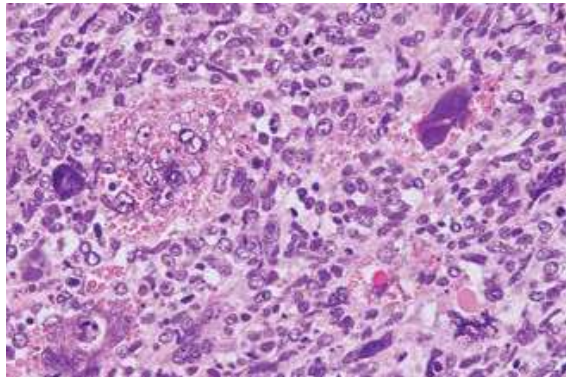


Figure 1-23

ANAPLASTIC NEPHROBLASTOMA

Enlarged hyperchromatic nuclei and multipolar mitotic figures (lower right) are the criteria for anaplasia. Anaplastic cells often contain eosinophilic cytoplasmic globules.

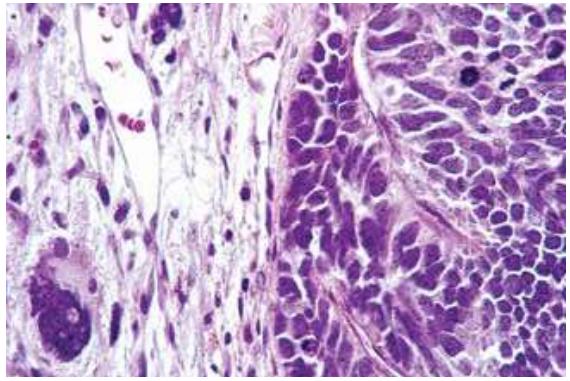


Figure 1-24

ANAPLASTIC NEPHROBLASTOMA

While anaplasia is typically evident in all components of nephroblastoma, it is easier to appreciate the enlarged hyperchromatic nuclei in the background of pale stroma (left) rather than in the blue blastema (right).

be enlarged. Enlarged nuclei are often easier to appreciate in the stroma, where they contrast well with a pale background (fig. 1-24). Similar degrees of nuclear enlargement are more difficult to appreciate in the blue background of the blastemal component (fig. 1-25).

The combination of nucleomegaly and hyperchromasia relative to the surrounding stroma reflects the increased DNA content of the polyploid anaplastic cells. Since injured nonanaplastic skeletal muscle nuclei often show these features, atypical mitoses must be present to exclude a degenerative process. Atypical mitotic figures must be large, with each arm larger than a normal metaphase plate. It is important to distinguish multipolar mitotic figures from minor mitotic abnormalities resulting from lagging of chromosomes on the anaphase spindle or uneven separation of a metaphase plate. The latter occasionally produce an X- or Y-shaped mitotic figure, but the total length of the X or Y structure is similar to that of a normal metaphase.

Anaplasia is rare during the first 2 years of life, but increases in prevalence to approximately 13 percent by 5 years of age. Anaplasia is 2 to 3 times more common in African Americans than

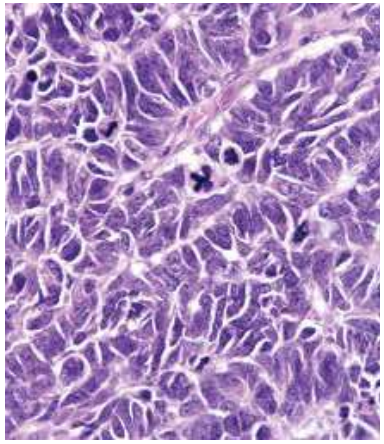


Figure 1-25

ANAPLASTIC NEPHROBLASTOMA

In this blastemal area, nuclear enlargement and hyperchromasia are best appreciated by comparing the neoplastic nuclei to the adjacent non-neoplastic endothelial cells. A multipolar mitotic figure is present in the center of the field; note that each arm of the abnormal mitosis is as large as that of a normal metaphase.

Caucasians. Anaplasia was thought to be an indicator of increased resistance to chemotherapy and not necessarily a marker of increased tumor aggressiveness, so patients with stage I anaplastic nephroblastoma and nephroblastoma with limited intrarenal foci of anaplasia (focal anaplasia) were predicted to have an excellent prognosis (fig. 1-26). This concept implies that the prognosis for a patient with anaplastic nephroblastoma is determined by the completeness of surgical removal of anaplastic cells. Indeed, anaplasia is most consistently associated with poor outcome in cases at advanced stage, where effective chemotherapy is needed to obliterate residual neoplastic cells not removed surgically. However, while anaplasia remains strongly associated with chemotherapy resistance, subsequent data on patients with stage I anaplastic nephroblastoma have suggested that anaplasia is also associated with increased aggressiveness (18).

Focal anaplasia imparts a prognosis that is intermediate between favorable histology and diffuse anaplasia, and the definition of focal anaplasia retains therapeutic implications on current protocols. Strict criteria for focal anaplasia are listed in Table 1-9. Anaplasia not proven to be focal is considered diffuse by default.

Anaplasia is closely correlated with the presence of *TP53* gene mutations. Whereas

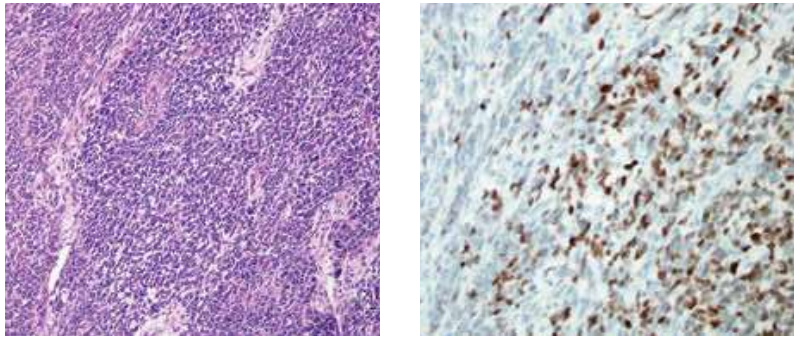


Figure 1-26

NEPHROBLASTOMA WITH FOCAL ANAPLASIA

Left: Enlarged hyperchromatic nuclei at the right of the field are compared to the nuclei at the left.
Right: The focal anaplasia correlates with focal strong labeling for TP53 protein by immunohistochemistry.

Table 1-9

HISTOLOGIC CRITERIA FOR FOCAL VERSUS DIFFUSE ANAPLASIA

Focal anaplasia
Clearly defined anaplasia within the primary tumor. It must be circumscribed and its perimeter completely examined (may require mapping of anaplastic foci that extend to the edge of tissue sections)
Anaplasia must be confined to the renal parenchyma
Anaplastic cells must not be present within vascular spaces
Absence of severe nuclear pleomorphism and hyperchromasia (severe "nuclear unrest") in nonanaplastic tumor
Diffuse anaplasia
Nonlocalized (multifocal) anaplasia
Anaplasia beyond the tumor capsule
Anaplastic cells in intrarenal or extrarenal vessels, renal sinus, extracapsular invasive sites, or metastatic deposits
Anaplasia that is focal, but with nuclear atypia approaching the criteria for anaplasia (so-called "nuclear unrest") present elsewhere in the tumor
Anaplasia not clearly demarcated from nonanaplastic tumor
Anaplasia present in a biopsy or other incomplete tumor sample
Anaplasia not meeting criteria for focal anaplasia

favorable histology nephroblastomas almost never harbor *TP53* mutations, most anaplastic nephroblastomas do (19). Furthermore, microdissection experiments have demonstrated that *TP53* mutations are usually restricted to the anaplastic portions of nephroblastomas with focal anaplasia (20). Because an apoptotic pathway induced by chemotherapy depends on a functional *TP53* gene, the association of *TP53* mutations with the resistance to chemotherapy that is the hallmark of anaplastic nephroblastoma makes sense. Recent studies show that *TP53* mutational status may better stratify risk in patients with diffuse anaplasia (21).

The term "nuclear unrest" has been used for those nephroblastomas demonstrating nuclear enlargement and hyperchromasia, but not meeting strict criteria for anaplasia, usually due to an absence of qualifying atypical mitotic figures. In a small biopsy, such findings are concerning for anaplasia in that the changes of diffuse anaplasia are not equally well developed in all areas of a tumor. In excised neoplasms, however, nuclear unrest has not demonstrated the adverse prognostic implications of anaplasia, and such cases are treated as favorable histology.

Nephroblastoma After Therapy. Chemotherapy-induced changes include necrosis, xanthomatous histiocytic foci, hemosiderin deposits, and fibrosis (fig. 1-27). Chemotherapy may also induce maturation of blastemal, epithelial, and stromal components, with striated muscle differentiation the most frequent. Remarkable responsiveness to chemotherapy has resulted in complete necrosis in some tumors; such cases are considered to be low risk in the SIOP protocol and may receive minimal treatment after surgery (22). In contrast, patients with tumors that retain a large amount of blastema despite therapy have a reduced prognosis and increased requirement for therapy.

Anaplastic foci typically remain unaffected by preoperative chemotherapy. Post-therapy resection specimens of nephroblastomas diagnosed as favorable histology on pretreatment biopsy often show nodules of viable anaplastic nephroblastoma in a background of treatment effect, suggesting that chemotherapy selected for the focal anaplastic clone. There is no evidence that preoperative chemotherapy promotes anaplasia.

Immunohistochemical Findings. The diversity of cell lines and degrees of differentiation in nephroblastoma impart a correspondingly varied immunohistochemical profile. Blastemal cells may or may not label for cytokeratin, typically show focal labeling for desmin, and are negative for other muscle markers like actin or myogenin. The profile of various differentiating cell lines depends on their patterns of differentiation. Immunoreactivity for WT1 protein (seen in approximately 80 percent of cases) is typically limited to the primitive blastemal and epithelial components of nephroblastoma; the differentiated epithelium and stroma are negative (fig. 1-28). However, WT1 also labels desmoplastic small round cell tumor (when carboxy-terminus-specific antibodies are

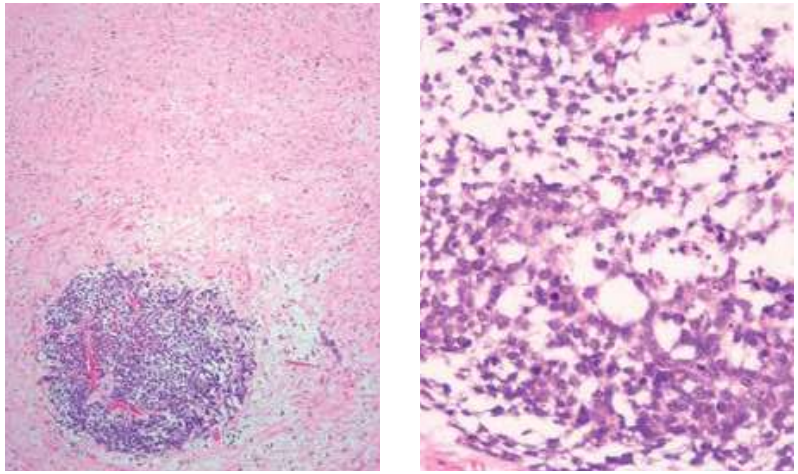


Figure 1-27

NEPHROBLASTOMA

Left: Following chemotherapy, large areas of the neoplasm may be replaced with necrosis, histiocytes, and fibrosis (top), while nodules of primitive nuclei remain (bottom).

Right: Actively proliferating blastemal cells after therapy indicate resistant tumor, and increased amounts of such resistant tumor adversely impact prognosis.

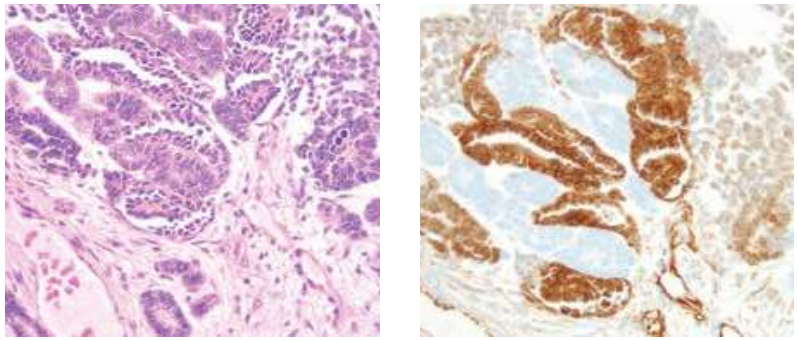


Figure 1-28

WT1 EXPRESSION IN NEPHROBLASTOMA

In a triphasic nephroblastoma (left), nuclear labeling for WT1 is typically most prominent in primitive blastemal and epithelial components, while more differentiated epithelium and stroma are negative (right).

used) and *CIC-DUX4* sarcomas. Similarly, PAX8 is consistently immunoreactive in the blastemal and epithelial components of nephroblastoma but can label other small round cell tumors such as Ewing sarcoma and clear cell sarcoma of the kidney.

Ultrastructural Findings. Ultrastructural study is rarely necessary to establish a diagnosis of nephroblastoma but may help distinguish nephroblastoma from other undifferentiated neoplasms. Cells that appear to be undifferentiated blastemal cells by light microscopy frequently show well-developed cell junctions, including desmosomes, which may account for the cell clustering and nuclear molding characteristic of blastemal cells. A flocculent coating of electron-dense material is often present on the cell surface (fig. 1-29).

Molecular Genetic Findings. Nephroblastomas are associated with a complex genetic profile that reflects genetic heterogeneity between different neoplasms. Nephroblastoma, like breast cancer, likely represents multiple distinct genetic entities that evolve via multiple pathways. As Beckwith postulated, these distinct genetic entities likely arise via neoplastic transformation of primitive nephroblastic elements at different stages of development, similar to the proposed pathogenesis of different subtypes of acute leukemia.

The *WT1* gene is mutated in approximately 20 percent of sporadic nephroblastomas. *WT1-mutated nephroblastomas* (but not *WT1* wild type tumors) frequently harbor *CTNNB1* mutations and almost all show β-catenin pathway activation (23). Some of these *WT1*-mutated nephroblastomas show squamous morules typical of other neoplasms associated with *CTNNB1* mutations (such as pancreatoblastoma). Epigenetic alterations at 11p15 are found in approximately 70 percent of cases, and are associated with concurrent perilobar nephrogenic rests. Other somatic genetic alterations identified in nephroblastoma include inactivation of a tumor suppressor gene on the X chromosome, *AMER1* (formerly known as *WTX*), in one-third of cases (24).

Differential Diagnosis. *Triphasic Nephroblastoma*. This pattern rarely presents a problem in diagnosis, except when small biopsy specimens are obtained from large retroperitoneal masses of uncertain origin. In this setting, other mixed neoplasms may deserve consideration, including

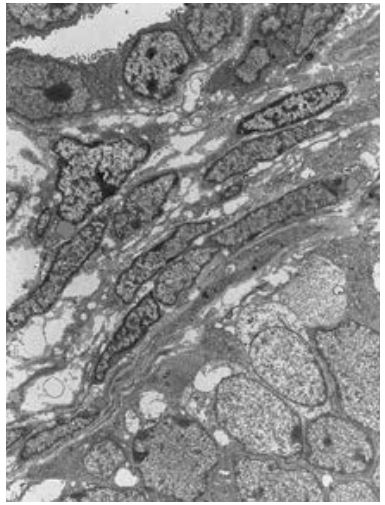


Figure 1-29

NEPHROBLASTOMA

Ultrastructural appearance of a triphasic neoplasm, with epithelial differentiation near the top of the field, stroma differentiation near the center, and blastemal cells near the bottom.

teratoma, hepatoblastoma, pancreatoblastoma, mesothelioma, synovial sarcoma, and intra-abdominal desmoplastic small round cell tumor. In the absence of nephrogenic differentiation or the distinctive blastemal aggregation patterns cited earlier, ancillary studies such as immunohistochemistry or molecular testing may be required to distinguish these lesions from nephroblastoma. Molecular detection of the distinctive *EWSR1-WT1* gene fusion of desmoplastic small round cell tumor or the *SS18-SSX* gene fusion of synovial sarcoma establish those diagnoses.

Nephroblastoma with extensive heterologous differentiation (*teratoid nephroblastoma*) is easily confused with immature teratoma (24a). Renal teratomas are extremely rare, and some of the reported pediatric cases likely represent teratoid nephroblastoma. Teratomas are characterized by heterologous organoid differentiation

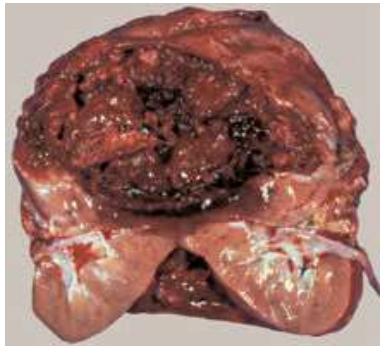


Figure 1-30

PRIMARY RENAL NEUROBLASTOMA

In infants, neuroblastoma may present as a mass that appears to arise from the kidney. Unlike nephroblastomas, these neoplasms are typically hemorrhagic and poorly delineated.

(recognizable differentiation into organs or body parts other than the one in which the tumor arises, such as luminal gastrointestinal tract wall or trachea). Nephroblastoma, like other mixed tumors, may contain one or more cell types found in another organ, but these are characterized by the random juxtaposition of various cell types, without the consistent structural organization characteristic of developing or mature organs.

Blastemal Nephroblastoma versus Other Small Blue Cell Tumors of Childhood. This problem is most likely to arise when dealing with biopsy specimens from metastatic sites or from large abdominal tumors of uncertain origin. The distinct aggregation patterns of blastemal nephroblastoma, the presence of nuclear molding, and the focal presence of tubular differentiation often reveal the diagnosis. The cellular neoplastic stroma of nephroblastoma (even when scant) helps distinguish it from other small round cell tumors.

Early tubular differentiation in nephroblastoma lacks lumens and therefore can sometimes be confused with rosettes of neuroblastoma or Ewing sarcoma (formerly, primitive neuroectodermal tumor [PNET]). However, early tubular structures usually have cells neatly aligned to form a single layer around the future lumen, whereas neuroblastic rosettes are aggregated more randomly around the central zone and are less consistently aligned. The presence of lumens even focally confirms tubular differentiation, whereas neurofibrils are diagnostic of a neuroblastic pseudorosette. Neuroblastic rosettes rarely do occur in nephroblastoma but usually only in teratoid nephroblastomas, which are not likely to be confused with neuroblastomas or Ewing sarcomas.

Any combination of immunohistochemistry, electron microscopy, molecular diagnostic techniques, cytogenetics, circulating tumor markers, and other special studies may be required to confirm the nature of a small blue cell tumor. For example, in infants, undifferentiated neuroblastoma may present as a mass centered in the kidney that is confused with blastemal nephroblastoma (figs. 1-30, 1-31). While a more hemorrhagic gross appearance and round nuclei with "salt and pepper" chromatin may suggest neuroblastoma, the best clue comes from evaluating serum or urine catecholamines. In teenagers, the diagnosis of Ewing sarcoma is more likely than blastemal nephroblastoma, and molecular studies to detect characteristic *EWSR1* gene fusions establish the diagnosis. Bilateral renal masses are an uncommon presentation for most neoplasms, with the exception of nephroblastoma, rhabdoid tumor, and lymphoma.

Epithelial-Predominant Nephroblastoma versus Papillary Renal Cell Carcinoma and Metanephric Adenoma. This dilemma is most often encountered in tumors from adolescents or adults. Low-grade papillary renal cell carcinomas may have a prominent tubular or solid component and resemble epithelial-predominant nephrogenic rests; epithelial-predominant nephroblastomas can have a predominantly papillary architecture. Molecular or cytogenetic studies show the increased copies of chromosomes 7 and 17 in low-grade (type 1) papillary renal cell carcinoma, and deletion of Y in tumors from male patients. Characteristic blastemal aggregation patterns or the presence of heterologous cell types confirms the diagnosis of nephroblastoma. Diffuse labeling for KRT7 (formerly CK7) is a useful marker for low-grade papillary renal cell carcinoma, but focal labeling is seen in

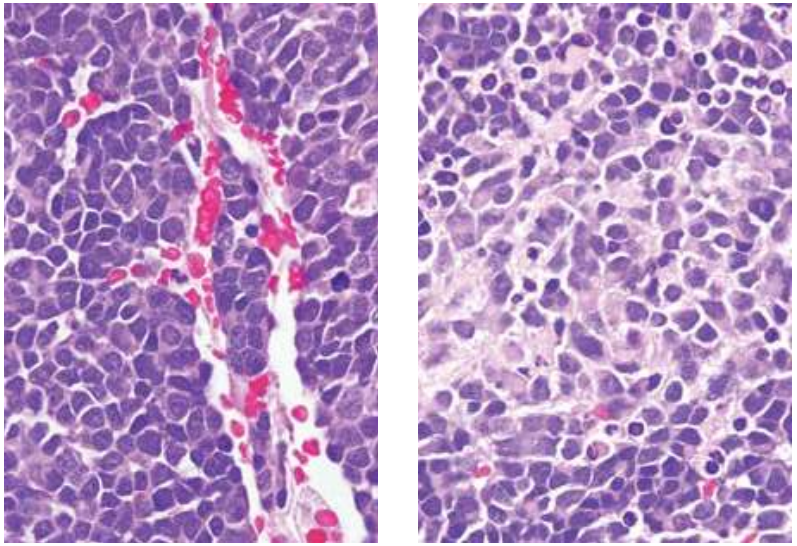


Figure 1-31

PRIMARY RENAL NEUROBLASTOMA

Left: Undifferentiated areas of neuroblastoma in infants may mimic blastemal Wilms tumor.
Right: Focal areas of ganglion cell differentiation and neuropil are evident.

many nephroblastomas. Nuclear labeling for WT1 protein distinguishes nephroblastoma, nephrogenic rests, and metanephric adenoma from papillary renal cell carcinoma because, of these four lesions, only the latter does not label.

Occasional epithelial-predominant nephroblastomas have differentiated areas that resemble metanephric adenoma (fig. 1-32), particularly after chemotherapy (fig. 1-33). Usually, other areas show a capsule and greater mitotic activity, which supports the diagnosis of nephroblastoma, as does the usual absence of *BRAF* V600E mutations that characterize most metanephric adenomas. Nevertheless, some nephroblastomas in children and adults that have areas that mimic metanephric adenoma do harbor the *BRAF* V600E mutations, and these neoplasms respond to therapy targeting BRAF (25). Conversely, rare otherwise typical metanephric adenomas harboring *BRAF* V600E mutations can have foci of mitotic activity that suggests nephroblastoma.

Stromal-Predominant Nephroblastoma versus Sarcomatous Renal Tumors. Much of this topic is discussed in the sections on these entities. Only selected points are added here. Most stromal-predominant nephroblastomas contain skeletal muscle, which is characteristic of the neoplasm and distinguishes it from other primary renal mesenchymal neoplasms such as congenital mesoblastic nephroma, rhabdoid tumor, and clear cell sarcoma of the kidney. A pediatric renal neoplasm containing skeletal muscle is assumed to be a nephroblastoma until proven otherwise. Rarely, true rhabdomyosarcomas arise in and overgrow an existing nephroblastoma. One such example is an alveolar rhabdomyosarcoma with a diagnostic *PAX-FOXO1* gene fusion arising in nephroblastoma.

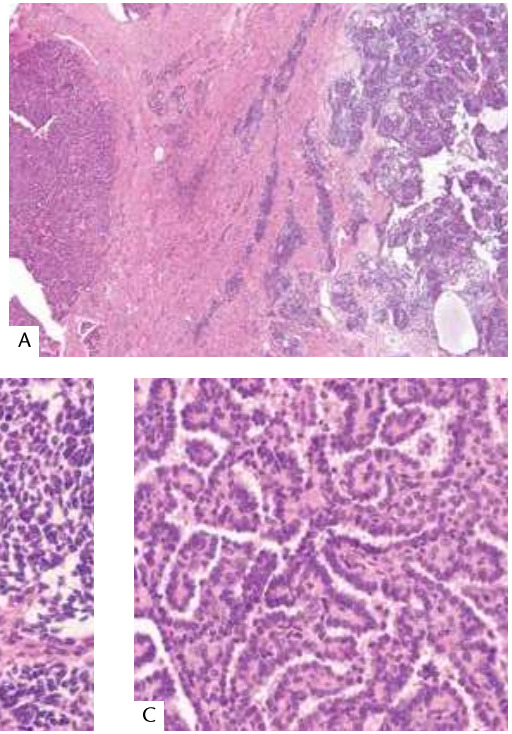


Figure 1-32

NEPHROBLASTOMA

Occasionally, an otherwise typical nephroblastoma (A,B) with abundant mitotic activity may have differentiated epithelial areas within it (C) that mimic metanephric adenoma.

When skeletal muscle is lacking, stromal-predominant nephroblastomas are more likely to be confused with congenital mesoblastic nephroma or clear cell sarcoma, particularly following chemotherapy. The diagnosis of a primary renal sarcoma following chemotherapy should always be made with caution, ideally after thorough examination of the post-therapy specimen and review of any pretreatment biopsy.

The spindle cell areas of a nephroblastoma may closely mimic the cytologic features of primary renal synovial sarcoma. Thorough sampling the specimen typically identifies areas more typical of nephroblastoma.

Other concerns include the recently described primary renal *CIC-DUX4* sarcomas, which also label for WT1, heightening the potential for misdiagnosis. These sarcomas have prominent nucleoli and genetic studies can definitively separate these lesions (26).

Nephroblastoma with Cysts versus Cystic Partially Differentiated Nephroblastoma. Cysts are common in nephroblastomas, and occasionally dominate the gross appearance. Cystic nephroblastoma is distinguished from cystic partially differentiated nephroblastoma by the presence of expansile nodules within the septa that mold the adjacent cysts, noted either grossly

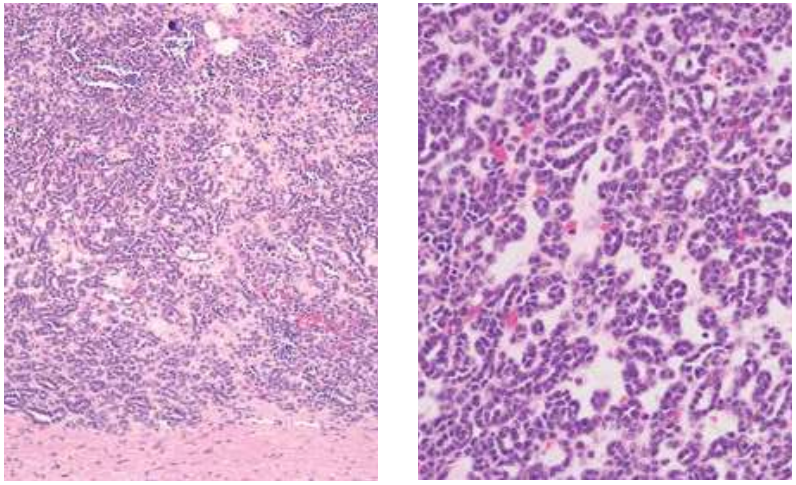


Figure 1-33

POST-THERAPY NEPHROBLASTOMA

Aside from encapsulation (left), this post-therapy specimen is morphologically identical to metanephric adenoma (right).

or microscopically (fig. 1-34). Simply stated, if the septa mold the cyst, the diagnosis is cystic nephroblastoma; if the cysts mold the septa, the diagnosis is cystic partially differentiated nephroblastoma. Parenthetically, in adults the same criteria are used to distinguish extensively cystic clear cell renal cell carcinoma from multilocular cystic renal cell neoplasm of low malignant potential (formerly known as multilocular cystic renal cell carcinoma).

Anaplasia versus Degenerative Nuclear Changes. Degenerative changes within skeletal muscle of a nephroblastoma, particularly following chemotherapy, can mimic the nucleomegaly and hyperchromasia of anaplastic nephroblastoma. However, such degenerating nuclei frequently show vacuolization, the cytoplasmic volume is also increased, imparting a relatively stable nucleus to cytoplasm ratio, and most importantly, mitotic figures are not found in such areas (fig. 1-35). These degenerative changes within the skeletal muscle components of a

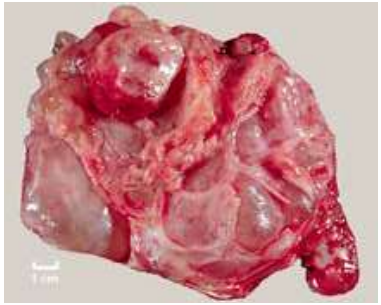


Figure 1-34

CYSTIC NEPHROBLASTOMA

This extensively cystic neoplasm in a child was thought to be compatible with cystic nephroma on imaging since no solid nodules were appreciated. Gross examination of the sectioned specimen revealed a 5-cm solid nodule of primitive nephroblastic elements (upper left), excluding cystic nephroma and establishing the diagnosis of cystic nephroblastoma.

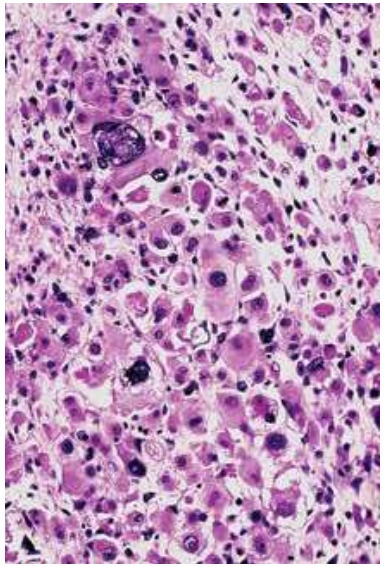


Figure 1-35

NEPHROBLASTOMA

Neoplastic cells with skeletal muscle differentiation may show striking nuclear enlargement, pleomorphism, and hyperchromasia, mimicking anaplasia. The concomitant increase in cytoplasm results in a relatively stable nucleus to cytoplasm ratio. No multipolar mitotic figures were present.

nephroblastoma parallel those commonly seen in degenerating benign skeletal muscle in other surgical specimens.

Treatment and Prognosis. Most nephroblastomas of low stage have favorable histology, and are associated with an excellent prognosis. The most significant unfavorable prognostic factors are high stage and the presence of anaplasia (18). Most blastemal tumors present at high stage but are very sensitive to therapy, so in pretreatment specimens the percentage of blastemal cells is not independently prognostic. Tumors that demonstrate extensive proliferating blastemal cells following preoperative chemotherapy, however, are associated with poor response to therapy and reduced survival (22,27,28). In SIOP protocols, these chemoresistant blastemal tumors are classified as "high risk" and are treated like anaplastic tumors.

Genetic studies that subclassify nephroblastomas into distinctive groups potentially may substratify risk (29–31). Nephroblastomas demonstrating loss of heterozygosity for chromosomes 1p and 16q are associated with a poor prognosis (32). Identification of these genetic alterations in current COG protocols triggers more intensive chemotherapy that may improve event-free survival, although overall survival is not improved and toxicities will likely increase. SIOP studies have found that gain of chromosome 1q represents a poor prognostic factor (33). Mutations in the SIX1/2 pathway and DROSHA/DGCR8 miRNA microprocessor complex have also been found in high-risk blastemal nephroblastomas (34).

The treatment of nephroblastoma is one of the major success stories of pediatric oncology. In general, patients with favorable histology low-stage tumors receive mild chemotherapy without radiation, while intensive chemotherapy and radiation are reserved for those with high-stage (stage III or IV) tumors and those with anaplasia. The overall 4-year survival rate for patients with favorable histology nephroblastomas is approximately 90 percent. The 4-year survival rates for those with stages I, II, III, and IV are 96, 91, 90, and 81 percent, respectively. Patients with diffuse anaplasia at stages II, III, and IV have survival rates of 70, 56, and 17 percent, respectively.

Survivors of nephroblastoma may have decreased pulmonary function, scoliosis, and infertility secondary to radiation therapy, or cardiac abnormalities secondary to doxorubicin therapy. Patients with bilateral neoplasms and those with underlying glomerular disease from Denys-Drash syndrome are predisposed to serious renal dysfunction. Intensive preoperative chemotherapy can maximize the chances of a successful bilateral nephron-sparing surgical approach that preserves renal function, with histologic response used to guide postoperative chemotherapy. Radiation and chemotherapy predispose to an increased incidence of secondary malignancy in these patients, approaching 2 percent at 15 years after diagnosis.

Table 1-10

FEATURES DISTINGUISHING PERILOBAR FROM INTRALOBAR RESTS

Feature	Perilobar Rests	Intralobar Rests
Position in lobe	Peripheral	Random
Margins	Sharp, demarcated; no native tubules in lesion	Irregular, intermingling with native tubules
Composition	Blastema and tubules predominate; stroma scant or sclerotic	Stroma often predominates
Distribution	Usually multifocal	Often unifocal

Table 1-11

INCIDENCE OF NEPHROGENIC RESTS IN ROUTINELY DISSECTED SPECIMENS

1% of pediatric autopsies
4% of dysplastic kidneys
30-40% of unilateral nephroblastoma cases
100% of bilateral nephroblastoma cases

NEPHROGENIC RESTS AND NEPHROBLASTOMATOSIS

Definition. *Nephrogenic rests* are abnormally persistent foci of embryonal cells (i.e., present after 36 weeks of gestation) that are potentially capable of developing into nephroblastoma. They are classified into perilobar and intralobar types (Table 1-10). The presence of diffuse or multifocal nephrogenic rests is termed *perilobar* or *intralobar nephroblastomatosis*. The presence of both perilobar nephrogenic rests and intralobar nephrogenic rests in the same kidney is termed *combined nephroblastomatosis*. Nephrogenic rests of either type can be found adjacent to a nephroblastoma or in the surrounding renal parenchyma.

General Features. Nephrogenic rests are found in approximately 1 percent of term infant autopsies (35–38). Perilobar nephrogenic rests (1 percent) are more frequent than intralobar nephrogenic rests (0.1 percent). Approximately 4 percent of dysplastic kidneys harbor perilobar nephrogenic rests. Nephrogenic rests are found in 25 to 40 percent of patients with nephroblastoma, and all cases of bilateral nephroblastoma (synchronous or metachronous) are associated with nephrogenic rests (Table 1-11).

Embryology. Understanding the significance of nephrogenic rests requires an understanding

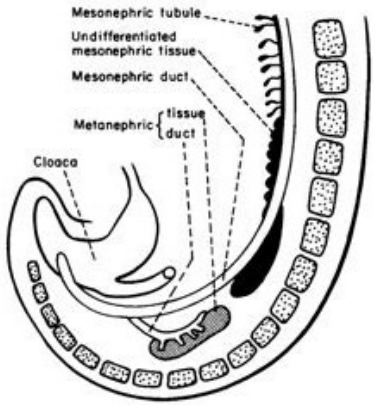


Figure 1-36

DEVELOPMENT OF THE METANEPHRIC KIDNEY

The ureteric bud arises from the caudal end of the mesonephric duct and gives rise to the ureter, renal pelvis, calices, and collecting ducts. The metanephric blastema, shown in fine grade striplings, is induced by the ureteric bud to form the nephrons and renal stroma.

of normal renal development. The permanent kidney begins development in the 4th week of gestation, when the metanephric duct (ureteric bud) penetrates into the lateral mesoderm, and induces it to condense into the metanephric blastema (fig. 1-36). From weeks 4 to 8, the ureteric bud successively branches and dilates to form the renal pelvis and collecting ducts. From weeks 8 to 36 of gestation, the ureteric bud's collecting ducts induce the metanephric

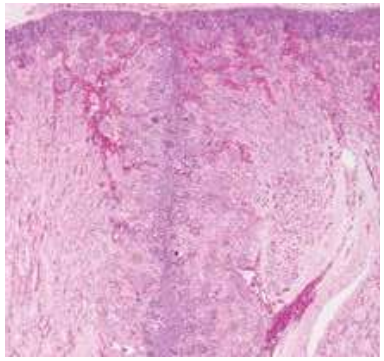


Figure 1-37

DEVELOPING KIDNEY IN A 20-WEEK GESTATION FETUS

Blastemal cells are situated at the cortical periphery of two abutting lobes. These are mainly subcapsular but extend down to the renal pelvis in a column of Bertin. The first cortical nephrons formed are at the corticomedullary junction, while the most recently formed are at the periphery of the lobe.

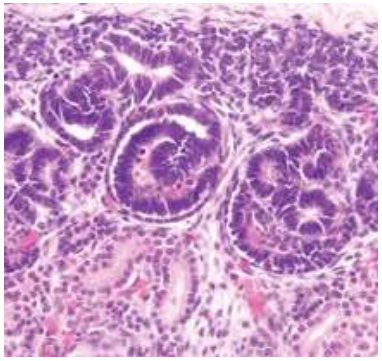


Figure 1-38

DEVELOPING KIDNEY IN A 20-WEEK GESTATION FETUS

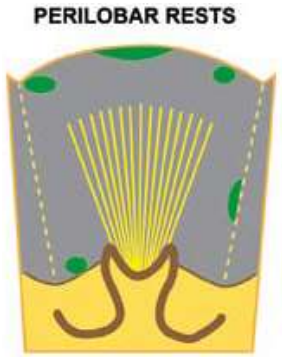
Subcapsular blastemal cells condense to form primitive tubular structures, which are penetrated by blood vessels to form immature glomeruli in a background of a spindle cell stroma. This is the embryonic step recapitulated by triphasic nephroblastoma.

blastema to form glomeruli and the remainder of the nephrons in each of eight lobes (fig. 1-37). Twelve generations of glomeruli are formed in this 28-week period, and this is the embryologic step that nephroblastoma recapitulates (fig. 1-38). Because the kidney develops in a centrifugal ("inside-out") pattern, nephrons located at the periphery of the cortical lobe have developed more recently than those located centrally near the medulla. Therefore, a disruption of early renal development (thought to be the etiology of intralobar nephrogenic rests) should affect the deeper cortex and potentially impact the entire cortical thickness, while a disruption that occurs in the last trimester of gestation (thought to be the etiology of perilobar nephrogenic rests) should affect only the most peripheral layers of cortical nephrons.

Gross Findings. Nephrogenic rests may appear paler than the surrounding normal kidney, but most are microscopic findings that are grossly unapparent. Hyperplastic nephrogenic rests (see below) may form clinically and grossly evident tumors.

Microscopic Findings. Perilobar nephrogenic rests, as described above, are thought to reflect abnormal renal development late during gestation and hence are usually located at the periphery of the renal lobe, which develops last. Therefore, perilobar nephrogenic rests are most frequently identified at the cortical subcapsular surface of the kidney, but may also be identified deep within the renal parenchyma along the cortical columns of Bertin, which represent the lateral edges of the renal lobes (fig. 1-39). They are well circumscribed but unencapsulated, and contain mainly blastemal and epithelial elements, whereas stroma is sparse or sclerotic.

Perilobar nephrogenic rests are further subclassified based on developmental fates into *dormant* (incipient), *regressing* (sclerosing), *obsolescent*, or *hyperplastic* categories, or may transform to nephroblastoma. Dormant nephrogenic rests remain unchanged in size or composition even for years, as microscopic foci of blastemal and tubular cells with minimal mitotic activity (fig. 1-40). Most nephrogenic rests become sclerotic, with prominent peritubular scarring (fig. 1-41).



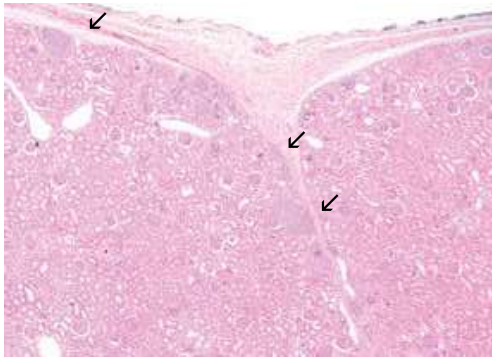


Figure 1-39

PERILOBAR NEPHROGENIC RESTS

Left: Perilobar nephrogenic rests (green) develop at the periphery of the renal lobe, are frequently lens shaped, and are well delineated from the renal parenchyma.

Right: Clusters of immature blastemal and tubular cells are present in the subcapsular areas and along a column of Bertin (arrows).

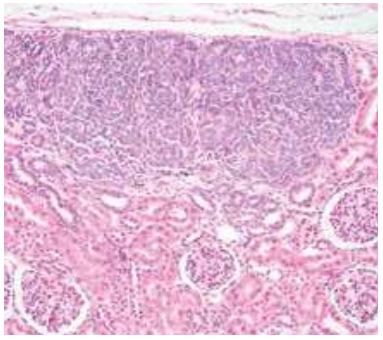


Figure 1-40

PERILOBAR NEPHROGENIC RESTS

This subcapsular perilobar nephrogenic rest demonstrates an absence of a capsule and the typical lens shape. It has minimal mitotic activity.

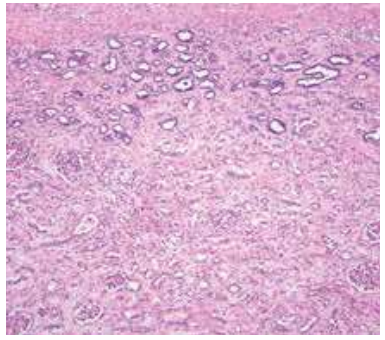


Figure 1-41

REGRESSING (SCLEROSING) PERILOBAR NEPHROGENIC REST

Prominent fibrosis replaces many of the primitive tubules, which are mitotically inactive.

The extreme form of this scarring is the obsolescent rest, which may be difficult to distinguish from nonspecific subcortical scarring (fig. 1-42).

Hyperplastic nephrogenic rests show coordinated proliferation of all susceptible cells of the rest, as distinguished from a clonal neoplastic

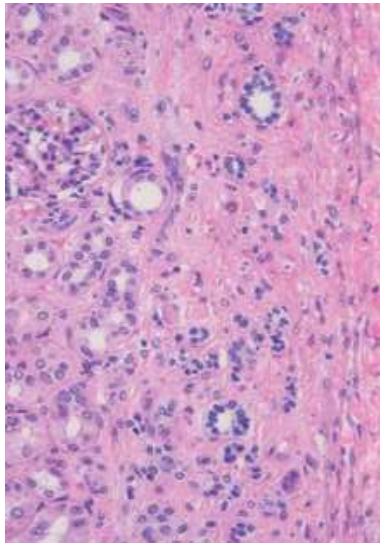


Figure 1-42

OBSOLESCENT PERILOBAR NEPHROGENIC REST

The presence of rare primitive tubules distinguishes this lesion from a nonspecific subcortical scar.

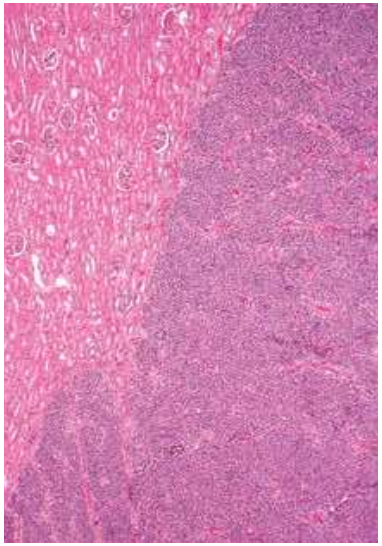


Figure 1-43

HYPERPLASTIC PERILOBAR NEPHROGENIC REST

The absence of a capsule and the nonspherical shape distinguish this lesion from an incipient nephroblastoma.

process originating in a single cell of the rest. Hyperplasia may produce large masses of blastemal and primitive tubular cells that have active growth and numerous mitotic figures, and a section or small biopsy from the interior of a hyperplastic nephrogenic rest may be indistinguishable from nephroblastoma. Hyperplasia involving all or most cells of a rest tends to preserve its original shape (fig. 1-43). When perilobar nephrogenic rests form a continuous layer of embryonal cells at the lobar surface, hyperplastic proliferation produces a thick "rind" of abnormal tissue at the renal surface. Ovoid and lenticular masses result from hyperplasia of perilobar nephrogenic rests that originally had these shapes. An irregularly shaped, multinodular appearance will result if only some of the cells are capable of proliferation.

Neoplastic induction is assumed to represent a clonal event originating in single cells of a rest, resulting in nephroblastoma or benign adenoma. Rapidly growing tumors originating at a single point (or cell) tend to grow equally in all directions, forming spherical, expansive nodules with compressed rest remnants often present at the periphery. This spherical shape contrasts with the typical ovoid shape of a hyperplastic nephrogenic rest. An additional important feature distinguishing actively hyperplastic perilobar nephrogenic rests from nephroblastoma is the usual absence of a pseudocapsule at the interface between hyperplastic nephrogenic rests and renal parenchyma (fig. 1-44). Some nephrogenic rests develop nodules of more epithelial cells, with increased pale eosinophilic cytoplasm and tubulopapillary

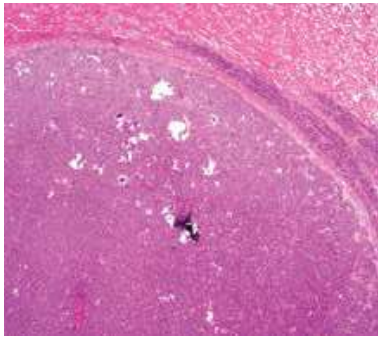


Figure 1-44

NEPHROBLASTOMA ARISING IN PERILOBAR NEPHROGENIC RESTS

The nephroblastoma is spherical and delineated from the perilobar rest from which it arose by a thin fibrous capsule.

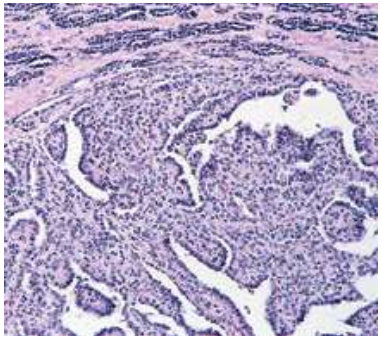


Figure 1-45

ADENOMATOUS CHANGE IN PERILOBAR NEPHROGENIC REST

The rest cells have acquired increased pale eosinophilic cytoplasm and have more prominent papillary architecture without significant mitotic activity.

architecture, termed *adenomatous change* (fig. 1-45). The significance of this is unclear but likely minimal.

Rarely, perilobar nephrogenic rests form a thick band ("crust"), replacing the renal cortex and resulting in massive renal enlargement (*diffuse hyperplastic perilobar nephroblastomatosis*) (fig. 1-46) (39). Diffuse hyperplastic perilobar nephroblastomatosis results in unilateral or bilateral massive renal enlargement (up to 1,500 g), and typically occurs in children between the ages of 1 and 3 years. The diffuse nature of the lesion and the more subtle involvement of the contralateral kidney in cases that clinically appear to be unilateral are radiologic clues to the diagnosis (fig. 1-47).

An individual rest commonly progresses through several stages sequentially. For example, an incipient or dormant rest may undergo hyperplastic proliferation, followed by a phase of growth arrest, maturation, and sclerosis (fig. 1-48). This results in a large but inactive-appearing lesion. Ultimately, one or more cells within the regressing rest may be induced to form nephroblastoma (figs. 1-49, 1-50). Anaplasia within perilobar nephrogenic rests was reported only once (40).

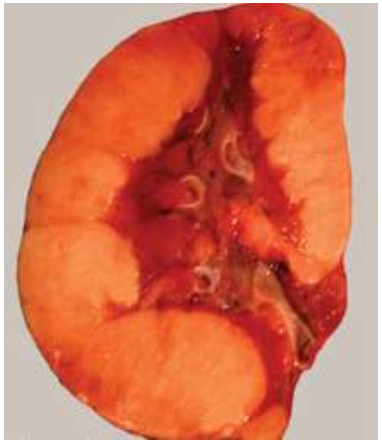


Figure 1-46

DIFFUSE HYPERPLASTIC PERILOBAR NEPHROBLASTOMATOSIS

The kidney is enlarged but preserves its reniform shape due to relatively uniform overgrowth of a peripheral rim of nephroblastic tissue.

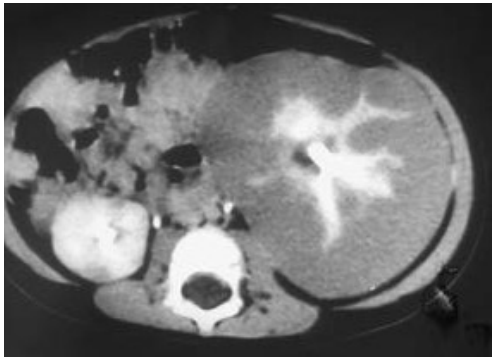


Figure 1-47

DIFFUSE HYPERPLASTIC PERILOBAR NEPHROBLASTOMATOSIS

The rind-like proliferation of tissue with homogeneous signal results in a markedly enlarged left kidney. A small, subcapsular oval lesion of the same density is seen in the right kidney, consistent with a perilobar nephrogenic rest.

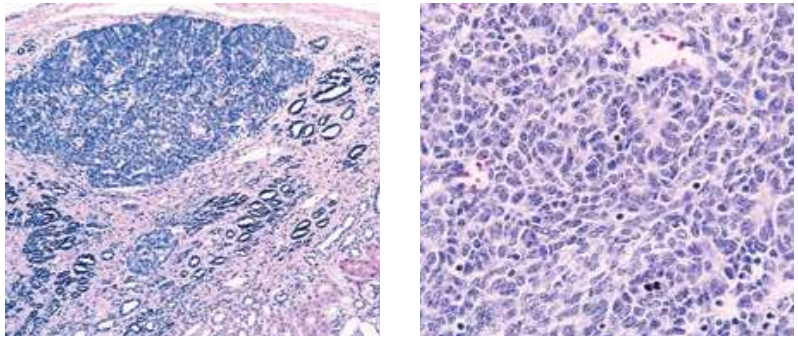


Figure 1-48

HYPERPLASTIC NODULE WITHIN A PERILOBAR NEPHROGENIC REST UNDERGOING SCLEROSIS

Fibrosis replaces some of the inactive primitive tubules at the right of the figure. The left contains a proliferative nodule of blastemal cells (left) which on higher power is morphologically indistinguishable from nephroblastoma (right).

In contrast to perilobar nephrogenic rests, intralobar nephrogenic rests are thought to reflect abnormal renal development earlier during gestation and thus typically are located in the central areas of the lobe (fig.1-51); however, intralobar nephrogenic rests may occur anywhere in the renal lobe, including the peripheral cortex. They are often single or sparse, poorly demarcated, and usually infiltrate native nephrons. They are mainly composed of stromal and epithelial elements (fig. 1-52). Intralobar nephrogenic rests are most often found at the nephroblastoma-kidney interface, where they can be misinterpreted as infiltrating tumor cells or be effaced by tumor compression. A helpful feature distinguishing intralobar nephrogenic rests at the edge of a nephroblastoma is the poorly defined, irregular outer border of the intralobar nephrogenic rest, which contrasts with the sharp, pushing interface between the nephroblastoma and the intralobar nephrogenic rest within which it arose (fig. 1-53).

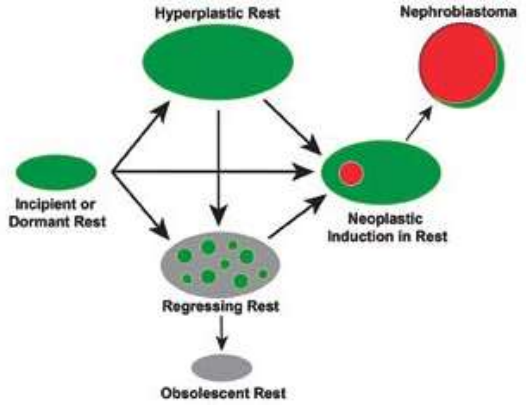


Figure 1-49

POTENTIAL FATES OF NEPHROGENIC RESTS

In this figure, gray areas represent regression whereas red nodules represent evolution to nephroblastoma. (Modified from fig. 4 in Beckwith JB. Precursor lesions of Wilms tumor: clinical and biological implications. Med Ped Oncology 1993;2:158-68.)

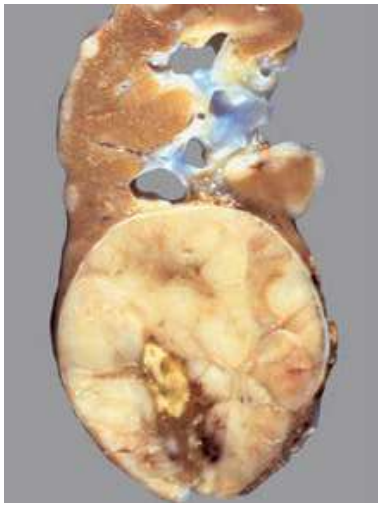


Figure 1-50

NEPHROBLASTOMA ARISING IN A PERILOBAR NEPHROGENIC REST

A large, rounded nephroblastoma occupies the lower pole. The smaller subcapsular lesions are hyperplastic rests, as suggested by their irregular shapes.

Figure 1-51

INTRALOBAR NEPHROGENIC REST

Intralobar rests are typically located centrally within the lobe, and are irregularly infiltrative of the renal parenchyma or the pelvic soft tissue.

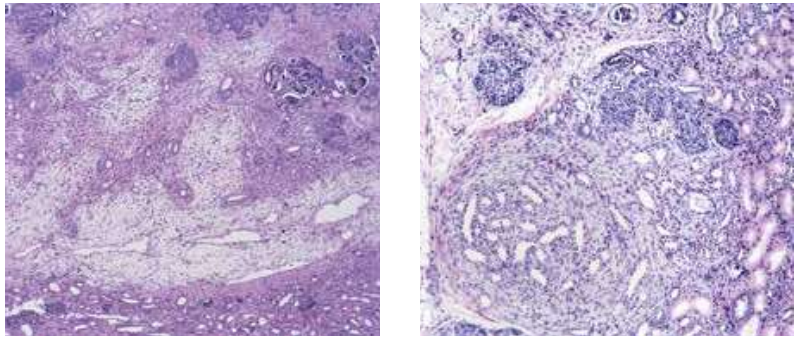


Figure 1-52

INTRALOBAR NEPHROGENIC REST

Left: At low power, the relatively hypocellular nature of the proliferation, and its prominent stromal component which intermingles with the renal parenchyma at the bottom, are appreciated.

Right: At high power, the intermingling of primitive elements of the intralobar rest (left) with the renal parenchyma (right) is seen. Adipose tissue is a common component of intralobar nephrogenic rests.

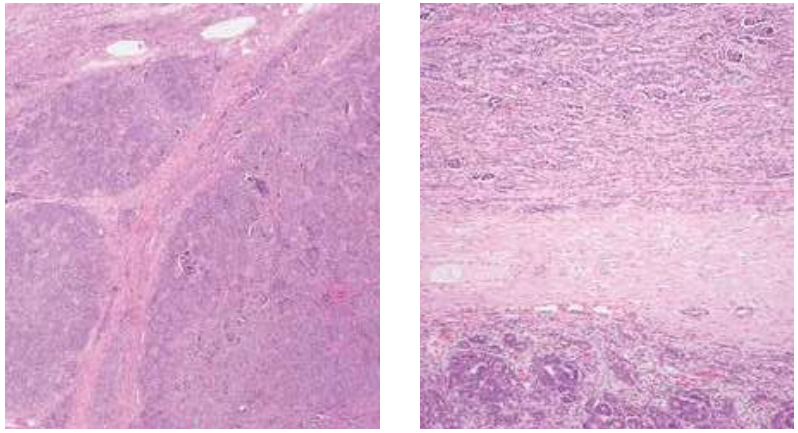
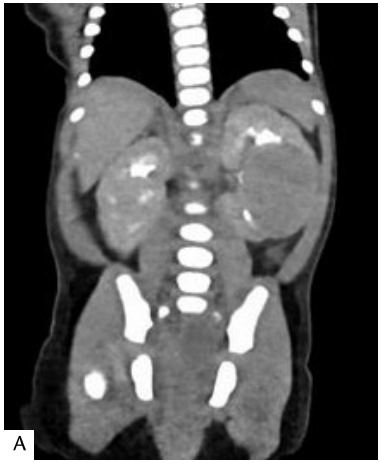


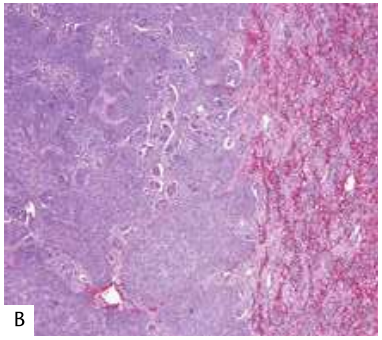
Figure 1-53

NEPHROBLASTOMA ARISING IN INTRALOBAR NEPHROGENIC RESTS

Left: The nephroblastoma on the right of figure is solid and well delineated by a thin fibrous capsule. The intralobar nephrogenic rest on the left of the figure contains fat and permeates the kidney at the upper left.

Right: At higher power, the nephroblastoma (bottom), its thick fibrous capsule (middle), and hyperplastic intralobar nephrogenic rest tissue intermingling with native tubules (top) are seen.





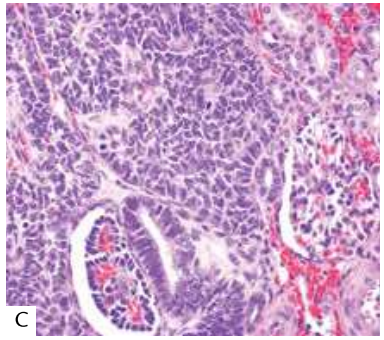


Figure 1-54

HYPERPLASTIC INTRALOBAR NEPHROGENIC REST ON CT SCAN

A: On CT scan, this mass lesion involves the left kidney unilaterally, and clinically was thought to represent a nephroblastoma. (Courtesy of Dr. D. Molavi, Baltimore, MD)

B: Histologically, the tumor appears rounded at low power.

C: It is distinguished from a nephroblastoma by its lack of encapsulation, despite its almost spherical shape.

Intralobar nephrogenic rests often also occur within the renal sinus, including in the walls of the pelvicalyceal system and ureter. Renal pelvic intralobar nephrogenic rests may have a botryoid appearance, similar to that of embryonal rhabdomyosarcoma.

Hyperplastic intralobar nephrogenic rests are also easily mistaken for nephroblastoma (fig. 1-54A). Two features help make this distinction. First, the permeative border of the intralobar nephrogenic rests contrasts with the encapsulated border of nephroblastoma (fig. 1-54B,C). Second, the histologic composition provides a clue: skeletal muscle is uncommon in intralobar nephrogenic rests but common in nephroblastoma, whereas fat is uncommon in nephroblastoma and common in intralobar nephrogenic rests.

The clinical features and histology of nephroblastoma may be determined by the type of nephrogenic rest from which it arose. Nephroblastomas arising in intralobar nephrogenic

Table 1-12

PREVALENCE OF NEPHROGENIC RESTS IN ROUTINELY DISSECTED KIDNEYS RESECTED FOR NEPHROBLASTOMA WITH ASSOCIATED SYNDROMES[a]

Syndrome	Perilobar Nephrogenic Rests (%)	Intralobar Nephrogenic Rests (%)
Beckwith-Wiedemann	70	47
WAGR	12	84
Denys-Drash	0	91

[a]Modified from Table 5 in Beckwith JB. Nephrogenic rests and the pathogenesis of Wilms tumor: developmental and clinical considerations. Am J Med Genet 1998;79:268-73.

rests often occur in young infants and tend to have prominent stroma, including skeletal muscle and cartilage. Nephroblastomas arising from perilobar nephrogenic rests occur in older children and tend to have predominant epithelial and blastemal elements.

Molecular Genetic Findings. Many of the same genetic alterations identified in nephroblastoma are also found in nephrogenic rests (41). *WT1* mutations and loss of heterozygosity are present in a subset of intralobar nephrogenic rests. Perilobar nephrogenic rests are associated with IGF2 overexpression.

Perilobar nephrogenic rests associated with hemihypertrophy reflect a loss of imprinting or loss of heterozygosity of *IGF2*. Intralobar nephrogenic rests are a marker of *WT1* mutations and thus are associated with Denys-Drash and WAGR syndromes (42,43). Patients with Beckwith-Wiedemann syndrome develop perilobar nephrogenic rests and intralobar nephrogenic rests, while those with Denys-Drash and WAGR syndromes almost exclusively develop intralobar nephrogenic rests (Table 1-12). Interestingly, perilobar nephrogenic rests are nearly absent in the Asian population, which correlates with their known earlier onset of nephroblastoma.

Differential Diagnosis. A small biopsy or fine needle aspirate from the center of a hyperplastic nephrogenic rest in diffuse hyperplastic nephroblastomatosis can be indistinguishable from nephroblastoma since the lesion's interface with the kidney is not sampled. In such circumstances, a diagnosis of "active nephroblastic proliferation" is appropriate, as it permits the oncologist to give chemotherapy appropriate for either diagnosis. Aside from nephroblastoma, only a few small incidental lesions commonly mimic nephrogenic rests.

The dysplastic medullary ray nodules (fig. 1-55) associated with Beckwith-Wiedemann syndrome are unencapsulated spindle cell proliferations which permeate adjacent collecting ducts, and can simulate intralobar nephrogenic rests. Embryonal hyperplasia (fig. 1-56) of Bowman capsular epithelium is commonly found in end-stage renal disease and simulates perilobar nephrogenic rests, although these lesions are typically periglomerular and not subcapsular as perilobar nephrogenic rests frequently are.

Treatment and Prognosis. In children who have undergone nephrectomy for nephroblastoma, the presence of nephrogenic rests (especially perilobar nephrogenic rests in children under 1 year of age) indicates increased risk of developing contralateral nephroblastoma (17). The risk decreases with increasing age at diagnosis, and stabilizes to approximately six-fold. An individual intralobar nephrogenic rest carries a greater risk of progressing to nephroblastoma than does an individual perilobar nephrogenic rest. However, because perilobar nephrogenic rests are almost always multiple and intralobar nephrogenic rests are typically single, the overall risks of nephroblastoma development in patients with perilobar nephrogenic rests and intralobar nephrogenic rests are similar.

When a carefully sampled kidney is free of rests, the risk of contralateral nephroblastoma is extremely low. This emphasizes the importance of sampling of nephrectomy specimens to include uninvolved kidney and tumor-kidney interfaces. The possibility of subsequent nephroblastoma developing in the contralateral kidney should be considered in planning the follow-up of patients whose nephrectomy specimens contain nephroblastoma and nephrogenic rests. More frequent ultrasonography (i.e., every 3 months versus the

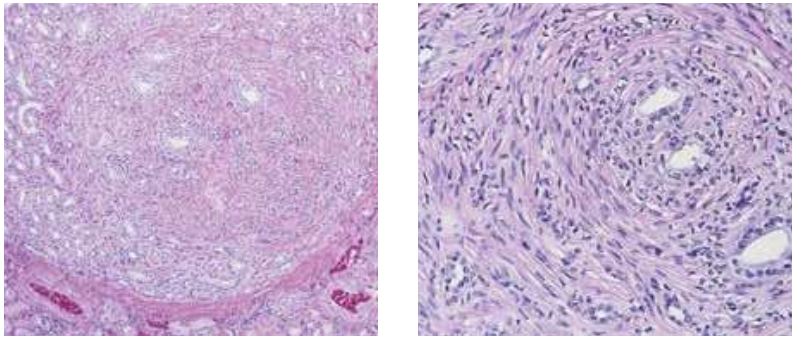


Figure 1-55

DYSPLASTIC MEDULLARY RAY NODULE

Left: This lesion is an extension of the malformed "Beckwith medulla" of the kidney in a patient with Beckwith-Wiedemann syndrome. The dysplastic medullary ray is rounded at intermediate power.

Right: It contains abnormally increased spindle cell stroma which encircles and displaces the normal collecting ducts.

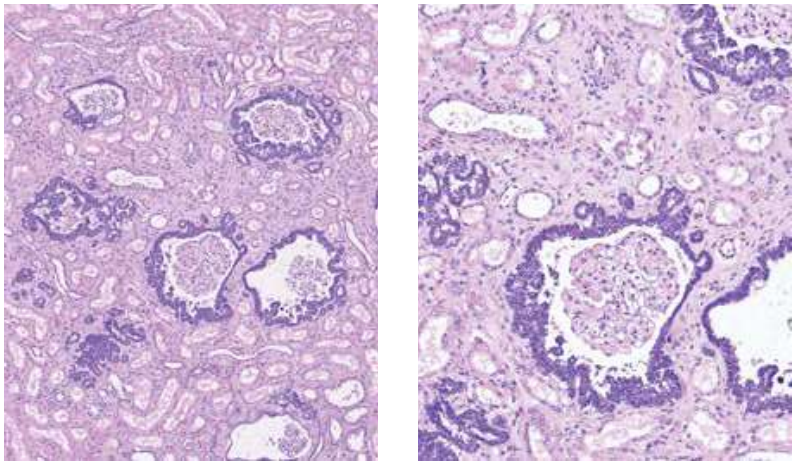


Figure 1-56

EMBRYONAL HYPERPLASIA OF BOWMAN CAPSULE EPITHELIUM

Left: The primitive epithelium is centered on glomeruli in end-stage renal disease. The clinical setting and nonsubcapsular location distinguish this from perilobar nephrogenic rests.

Right: The primitive tubular epithelium is similar to that of perilobar nephrogenic rests.

Figure 1-57

CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA

Gross photograph of the sectioned surface.

usual every 6 months) is often recommended when nephrogenic rests are identified.

Diffuse hyperplastic nephroblastomatosis is associated with a high risk of developing multiple nephroblastomas as well as anaplastic nephroblastomas. Approximately 50 percent of patients with diffuse hyperplastic perilobar nephroblastomatosis who receive chemotherapy are cured and never develop subsequent renal neoplasms. The remaining patients typically develop repeated cycles of hyperplasia and regression of their nephrogenic rests over a period of 5 to 10 years, frequently associated with the development of multiple nephroblastomas. Approximately one third of these patients develop an anaplastic nephroblastoma, in part due to the multitude of nephroblastomas that develop in each patient, so these nephroblastomas must be closely monitored for responsiveness to therapy. Nephroblastomas that grow through chemotherapy are more likely to be anaplastic.

Chemotherapy is the usual initial treatment for diffuse hyperplastic nephroblastomatosis. Chemotherapy reduces the compressive burden of nephroblastic tissue, which enables normalization of renal function, and reduces the number of proliferating cells that progress to nephroblastoma. These lesions must be carefully monitored for responsiveness to therapy by serial imaging studies to enable early detection of nephroblastoma (44), particularly given the higher percentage of patients who develop anaplastic nephroblastomas. Prompt therapy can minimize the amount of native kidney that requires surgical excision, thereby maximizing the preservation of renal function. If improperly managed with unnecessarily extensive surgery, many of these patients develop renal insufficiency.

CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA

Definition. *Cystic partially differentiated nephroblastoma* is a multilocular, exclusively cystic neoplasm of very young children that contains nephroblastomatous tissue.

Clinical Features. Cystic partially differentiated nephroblastoma occurs more commonly in boys than girls. Most patients are less than 24 months old.

Gross Findings. Cystic partially differentiated nephroblastomas often are large, especially considering the patients' age, ranging up to 19 cm in diameter (mean, 10 cm). They are well circumscribed and consist entirely of cysts of variable size; the septa are thin and there are no expansile, solid nodules to alter the rounded contour of the cysts (fig. 1-57).

Microscopic Findings. Cystic partially differentiated nephroblastoma is composed entirely of cysts separated by septa (fig. 1-58) (45–47). The cysts are lined by flattened, cuboidal, or hobnail epithelium, or are denuded. The septa are variably cellular and contain

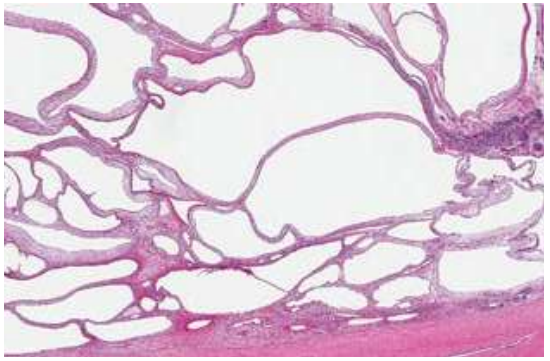


Figure 1-58

CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA

The lesion is well delineated and entirely cystic, with thin septa that are molded by the cysts. A nonexpansile cluster of primitive nephroblastic elements is evident at the right. (Courtesy of Dr. G. Vujanic, Cardiff, UK)

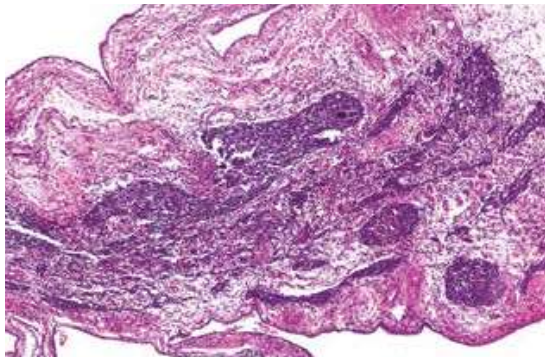


Figure 1-59

CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA

Immature nephroblastic elements are confined to the wall of a cyst and do not form an expansile nodule. (Courtesy of Dr. G. Vujanic, Cardiff, UK)

undifferentiated and differentiated mesenchyme (often skeletal muscle, occasionally cartilage or fat), islands of blastema, and nephroblastomatous epithelial elements (fig. 1-59) (46). Focally, the septal elements may protrude into the cysts in microscopic papillary folds. The epithelial components consist mainly of mature and immature tubules and small papillae resembling immature glomeruli.

Molecular Genetic Findings. Cystic partially differentiated nephroblastomas have historically been considered part of the spectrum of cystic nephroblastoma, the most extreme form of which was pediatric cystic nephroma. The latter is an exclusively cystic renal neoplasm that lacks nephroblastomatous tissue. However, recent genetic studies have shown that pediatric cystic nephroma, but not cystic partially differentiated nephroblastoma, harbors *DICER1* mutations, suggesting that these two neoplasms are distinct and unrelated (48).

Differential Diagnosis. The distinction of cystic partially differentiated nephroblastoma from cystic nephroblastoma is discussed in the section on nephroblastoma.

Treatment and Prognosis. Surgery is almost always curative (49,50); patients with stage I disease need no adjuvant chemotherapy (50). Rare recurrences have been reported as a complication of incomplete resection (47) or tumor rupture (51).

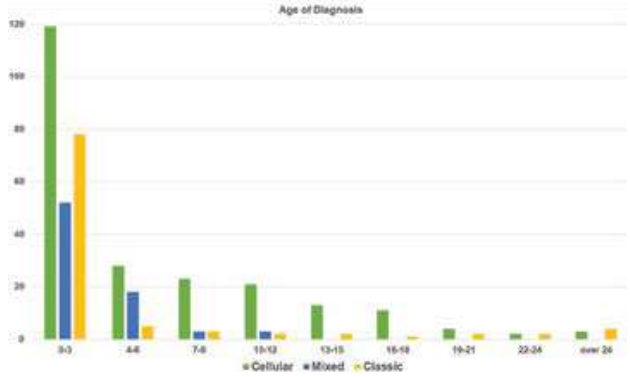


Figure 1-60

CONGENITAL MESOBLASTIC NEPHROMA

Age distribution curve for patients with congenital mesoblastic nephroma based on cases at the National Wilms Tumor Study Group Pathology Center.

CONGENITAL MESOBLASTIC NEPHROMA

Definition. *Congenital mesoblastic nephromas* are low-grade fibroblastic neoplasms of the infantile renal sinus, divided into classic and cellular types. "Adult mesoblastic nephroma" was a term previously used in some publications; however, these were a mixture of unrelated adult neoplasms including mixed epithelial and stromal tumors and renal synovial sarcoma.

Clinical Features. Congenital mesoblastic nephroma comprises 2 to 3 percent of pediatric renal tumors. It is the most common congenital renal neoplasm, and is the most common renal neoplasm in the first 3 months of life. Ninety percent of cases are diagnosed in the first year of life. The median age at diagnosis is 2 months. *Classic congenital mesoblastic nephroma* typically presents earlier, usually in the first few weeks of life, while *cellular congenital mesoblastic nephroma* often presents in the first few months (52). The diagnosis of congenital mesoblastic nephroma should be considered suspect in any patient beyond the second year of life (fig. 1-60).

The typical presentation of congenital mesoblastic nephroma has been an abdominal mass. However, many are now detected during fetal sonography. Hydramnios is common during gestation, and nonimmunologic fetal hydrops has been reported. Hyperreninism resulting from renin production by entrapped juxtaglomerular cells, hypercalcemia secondary to prostaglandin E production by the neoplasm, and coagulopathy or shock from tumor rupture during delivery also have been reported.

Gross Findings. Almost all congenital mesoblastic nephromas are located centrally and involve the renal sinus. The renal sinus and adjacent structures are major sites of extrarenal spread. The medial margin of the resection specimen is very important when handling potential congenital mesoblastic nephroma specimens. This is not easy since the medial specimen margin is often irregular and difficult to evaluate, and it is rarely possible to be certain that it is free of involvement by congenital mesoblastic nephroma (fig. 1-61).

The gross features of classic and cellular congenital mesoblastic nephromas are usually different. Pure classic congenital mesoblastic nephromas are usually small, with nephrectomy specimens rarely exceeding 100 g. Cellular congenital mesoblastic nephromas may be very large, with nephrectomy specimens sometimes exceeding 1 kg. On cut section, classic congenital mesoblastic nephroma has a firm, whorled texture (fig. 1-62). In contrast, cellular congenital mesoblastic nephromas are more typically soft, cystic, and hemorrhagic (fig. 1-63).

Microscopic Findings. As mentioned, congenital mesoblastic nephroma is generally categorized into a classic fibromatosis-like subtype

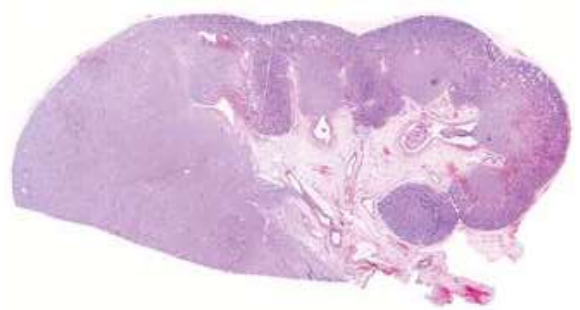


Figure 1-61

CONGENITAL MESOBLASTIC NEPHROMA, CLASSIC TYPE

The tumor extensively involves renal sinus soft tissue, making assessment of the medial margin problematic.

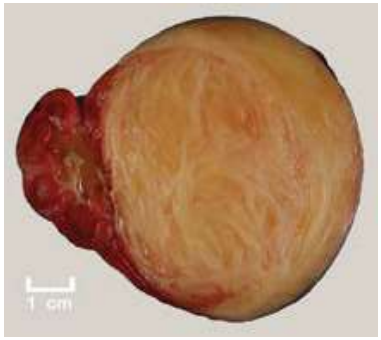


Figure 1-62

CONGENITAL MESOBLATIC NEPHROMA, CLASSIC TYPE

The lesion is fibrous and ill-defined, permeating the native kidney.

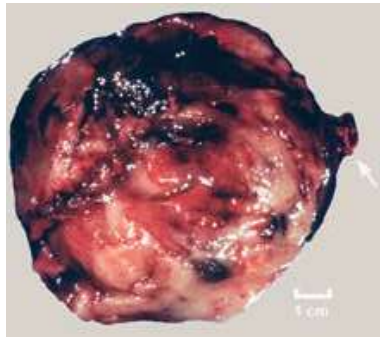


Figure 1-63

CONGENITAL MESOBLASTIC NEPHROMA, CELLULAR TYPE

The neoplasm is fleshy and hemorrhagic, and nearly obliterates the surrounding kidney and adrenal gland (arrow).

and a cellular infantile fibrosarcoma–like subtype. Variable combinations of these patterns are occasionally seen, as areas similar to the cellular pattern occur in a background of areas similar to the classic pattern (*mixed congenital mesoblastic nephroma*). Molecular data confirm the distinctive natures of classic and cellular congenital mesoblastic nephromas (Table 1-13).

Although classic congenital mesoblastic nephroma was the first subtype described, only 24 percent of tumors are of the pure classic pattern. Classic congenital mesoblastic nephroma is morphologically identical to infantile fibromatosis of the renal sinus (53). Long tongues of tumor dissect and entrap islands of renal parenchyma and sinus soft tissue (fig. 1-64). The tumors are composed of interlacing fascicles of fibroblastic cells of low cellularity with thin tapered nuclei, pink cytoplasm, low mitotic activity, and abundant collagen deposition (fig. 1-65). Hemangiopericytomatous vasculature is common (fig. 1-66). The permeation but not compression of the native renal parenchyma suggests that classic congenital mesoblastic

Table 1-13

CLASSIC VERSUS CELLULAR CONGENITAL MESOBLASTIC NEPHROMA

Feature	Classic Congenital Mesoblastic Nephroma	Cellular Congenital Mesoblastic Nephroma
Median age at diagnosis	Weeks	Months
Median weight	Usually <100g	Often >1kg
Cut section	Whorled, fibrous	Fleshy, cystic, hemorrhagic
Border with native kidney	Permeative	Pushing
Soft tissue analog	Infantile fibromatosis	Infantile fibrosarcoma
ETV6-NTRK3 fusion	Absent	Present
EGFR internal tandem duplication	Usually present	Usually absent

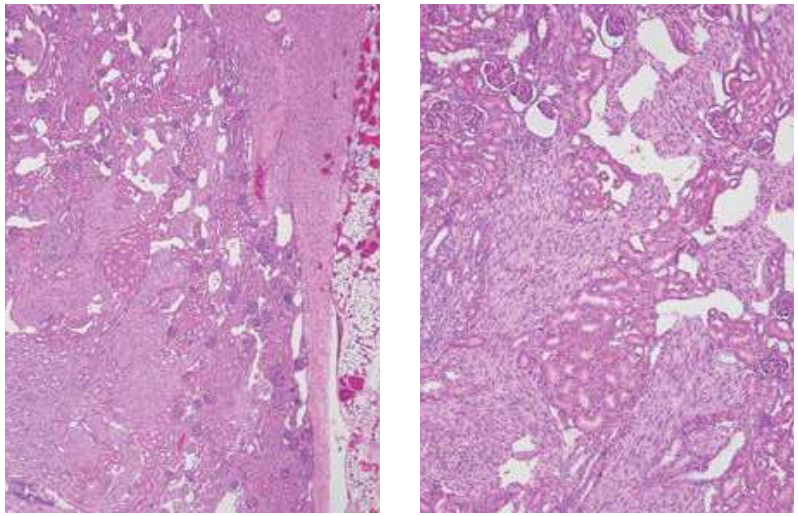


Figure 1-64

CONGENITAL MESOBLASTIC NEPHROMA, CLASSIC TYPE

Left: The spindle cell proliferation dissects islands of native tubules, and infiltrates the cortical capsule to extend into the perirenal fat.

Right: This neoplasm intermingles with islands of seemingly unaffected renal parenchyma.

nephroma and the developing kidney grow together in utero. Indeed, small islands of cartilage are often found at the advancing edge of the tumor or in the surrounding renal parenchyma, representing dysplasia, a result of in utero obstruction of the developing kidney (fig. 1-67). Foci of extramedullary hematopoiesis also are common (fig. 1-68).

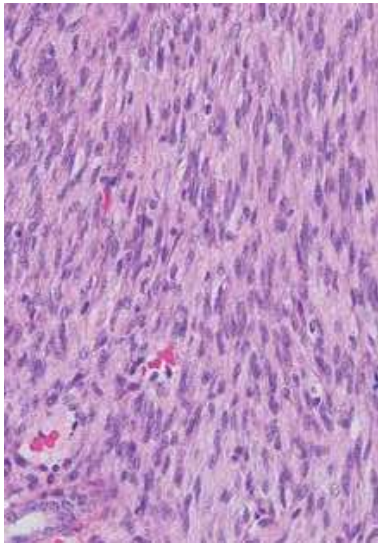


Figure 1-65

CONGENITAL MESOBLASTIC NEPHROMA, CLASSIC TYPE

Fascicles of bland spindle cells associated with collagen, similar to the morphology of fibromatosis.

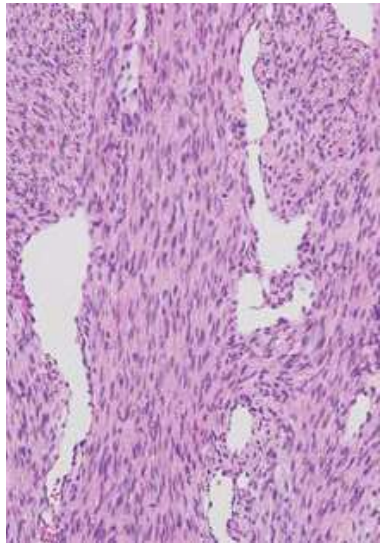


Figure 1-66

CONGENITAL MESOBLASTIC NEPHROMA, CLASSIC TYPE

The neoplastic cells indent dilated intratumoral vessels. Historically this had been termed "hemangiopericytomatous" vasculature.

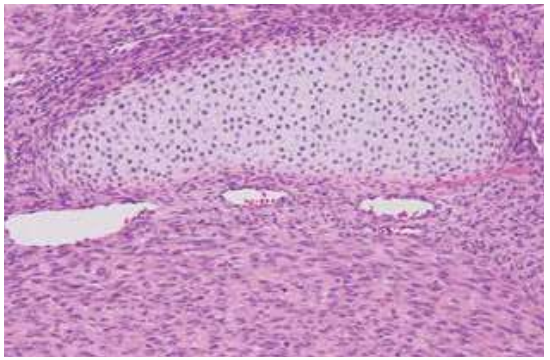


Figure 1-67

CONGENITAL MESOBLASTIC NEPHROMA, CLASSIC TYPE

An island of cartilage in the neoplasm represents renal dysplasia.

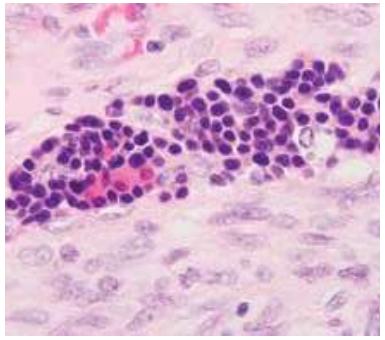


Figure 1-68

CONGENITAL MESOBLASTIC NEPHROMA, CLASSIC TYPE

Extramedullary hematopoiesis is common within these neoplasms.

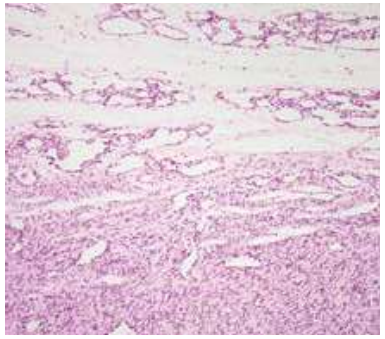


Figure 1-69

CONGENITAL MESOBLASTIC NEPHROMA, CLASSIC TYPE

When classic congenital mesoblastic nephroma penetrates through the renal capsule, it typically induces a prominent angiomatous capillary vascular proliferation.

In addition to involving the renal sinus and adjacent soft tissues, classic congenital mesoblastic nephroma also frequently extends into perirenal soft tissue, where its advancing edge often induces angiomatous vascular proliferation (fig. 1-69). The interdigitating borders of the lesion entrap renal tubules and glomeruli, and the entrapped epithelial cells often undergo "embryonal metaplasia," producing tall cuboidal to columnar cells that should not be misinterpreted as evidence of nephroblastoma (fig. 1-70).

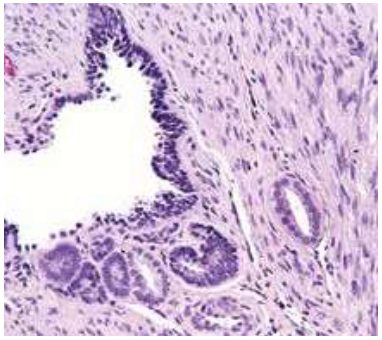


Figure 1-70

CONGENITAL MESOBLASTIC NEPHROMA, CLASSIC TYPE

Embryonal hyperplasia of entrapped renal tubules (left) is common, inviting confusion with biphasic nephroblastoma.

Cellular congenital mesoblastic nephroma (66 percent of cases) is morphologically identical to infantile fibrosarcoma. These tumors have a pushing border (fig. 1-71A), and are composed of poorly formed fascicles that give way to solid sheets (fig. 1-71B). The nuclei are nearly rectangular, but characteristically, one end is pointed (fig. 1-71C). These tumors show high mitotic rates and frequently feature geographic areas of necrosis (fig. 1-71D). As with classic congenital mesoblastic nephroma, intratumoral blood vessels frequently have a staghorn, hemangiopericytomatous pattern (fig. 1-72).

Cellular congenital mesoblastic nephroma has two distinct cytologic appearances. The most common is a "plump cell" pattern, characterized by large spindle-shaped or polygonal cells with abundant cytoplasm and variably enlarged, vesicular nuclei that may contain large

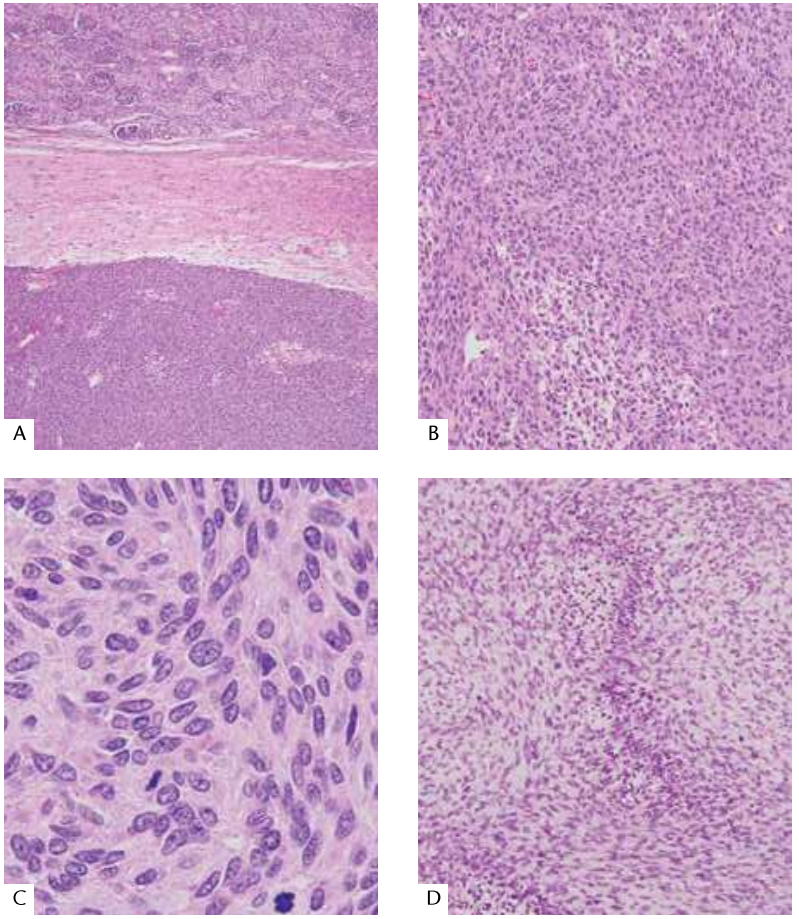


Figure 1-71

CONGENITAL MESOBLASTIC NEPHROMA, CELLULAR TYPE

A: This cellular neoplasm is well delineated from the kidney at the top.
B: Cellular congenital mesoblastic nephroma is typically composed of monomorphic plump spindle cells, often with no defined architecture.
C: The neoplastic cells have ill-defined pink cytoplasm, and nuclei that often taper at one end but not the other.
D: The neoplasm shows palisaded necrosis, similar to that seen in glioblastoma multiforme.

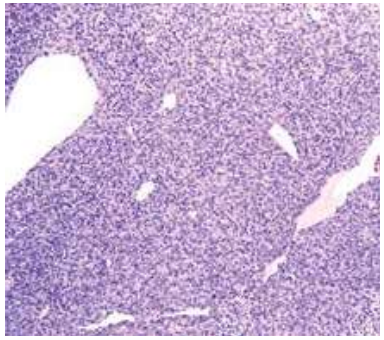


Figure 1-72

CONGENITAL MESOBLASTIC NEPHROMA, CELLULAR TYPE

The neoplastic cells indent dilated intratumoral vessels. Historically this had been termed "hemangiopericytomatous" vasculature.

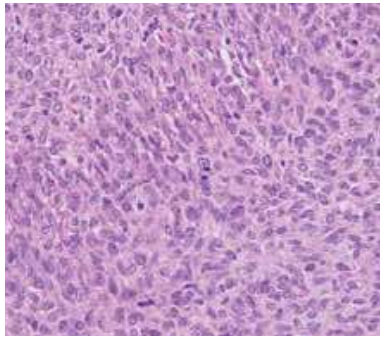


Figure 1-73

CONGENITAL MESOBLASTIC NEPHROMA, CELLULAR TYPE

In the "plump cell" pattern, the spindle cells have abundant eosinophilic cytoplasm, and nuclei have vesicular chromatin with occasionally prominent nucleoli.

nucleoli (fig. 1-73). The prominent nucleoli and cytoplasm of this subtype, along with the infantile age at diagnosis, can lead to confusion with rhabdoid tumor. The morphologic features favoring plump cell congenital mesoblastic nephroma over rhabdoid tumor are less invasive tumor margins, with a tendency toward encapsulation; predominantly spindle-shaped versus polygonal cells; and usual absence of cytoplasmic inclusions. The other, less commonly encountered histologic subtype of cellular congenital mesoblastic nephroma is a small blue cell variant with minimal cytoplasm (fig. 1-74).

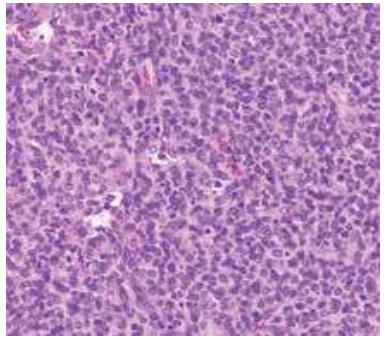


Figure 1-74

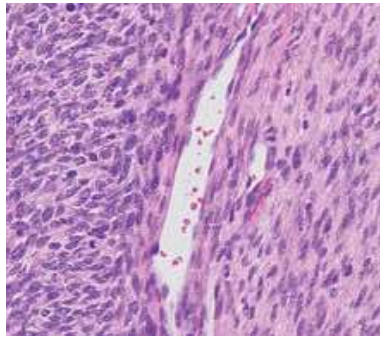
CONGENITAL MESOBLASTIC NEPHROMA, CELLULAR TYPE

In the less common "blue cell" variant, the smaller, rounded neoplastic cells have minimal cytoplasm.

Mixed congenital mesoblastic nephroma (10 percent of cases) has features of both classic and cellular congenital mesoblastic nephromas (fig. 1-75). Many mixed congenital mesoblastic nephromas are the renal counterparts of composite fibromatosis, an infantile fibrosarcoma-like cellular pattern seen in some cases of infantile fibromatosis or myofibromatosis.

Congenital mesoblastic nephromas are myofibroblastic neoplasms, so not surprisingly, they are often immunoreactive for actin and infrequently label for desmin; CD34 is typically nonreactive. Ultrastructurally, congenital mesoblastic nephromas show abundant rough endoplasmic reticulum with branching and anastomosing profiles and primitive cell junctions (fig. 1-76) (54).

Molecular Genetic Findings. Cellular congenital mesoblastic nephroma, in contrast



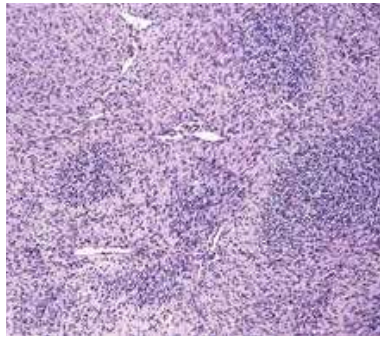


Figure 1-75

CONGENITAL MESOBLASTIC NEPHROMA, MIXED TYPE

Left: In the mixed pattern, areas morphologically identical to the cellular type (left) abut less cellular, more fascicular areas identical to the classic type (right).

Right: In mixed pattern congenital mesoblastic nephroma, small cellular foci are often multifocal within an otherwise classic pattern neoplasm.

Table 1-14

INFANTILE FIBROBLASTIC NEOPLASMS OF THE KIDNEY AND THEIR SOFT TISSUE COUNTERPARTS

Kidney	Soft Tissue
Classic congenital mesoblastic nephroma	Infantile fibromatosis
Cellular congenital mesoblastic nephroma	Infantile fibrosarcoma
Mixed congenital mesoblastic nephroma	Composite fibromatosis

to classic congenital mesoblastic nephroma, harbors a specific chromosome translocation, t(12;15)(p13;q25), which results in a fusion of the *ETV6* and *NTRK3* genes. The same chromosome translocation and gene fusion was first identified in infantile fibrosarcoma but is not present in infantile fibromatosis or classic congenital mesoblastic nephroma (55–57). Thus, cellular congenital mesoblastic nephroma and infantile fibrosarcoma are identical neoplasms.

Like classic congenital mesoblastic nephroma, most mixed congenital mesoblastic nephromas lack the *ETV6-NTRK3* gene fusion (58,59), which is analogous to composite fibromatosis/fibrosarcoma of soft tissue (Table 1-14) (60). It is

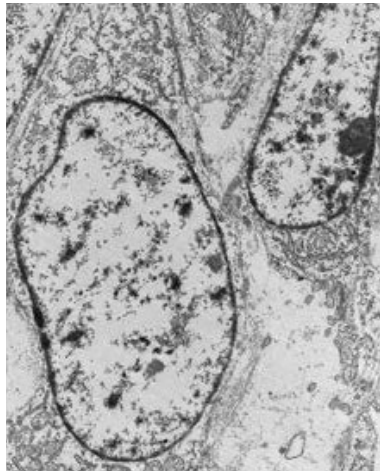


Figure 1-76

CONGENITAL MESOBLASTIC NEPHROMA

Electron micrograph demonstrates prominent rough endoplasmic reticulum typical of fibroblastic cells.

Table 1-15

CONGENITAL MESOBLASTIC NEPHROMA VERSUS CLEAR CELL SARCOMA OF KIDNEY

Feature	Congenital Mesoblastic Nephroma	Clear Cell Sarcoma of Kidney
Age	Usually <3 years	Median 3 years, can be higher
Border with native kidney	Entraps islands of native renal tubules (classic type) or pushing (cellular type)	Entraps single native renal tubules
Chromatin	Coarse	Fine
Prominent nucleoli	Sometimes	Never
Variant patterns	No	Yes
BCOR immunolabeling	None or only focal	Strong and diffuse

likely that some mixed congenital mesoblastic nephromas that have *ETV6-NTRK3* gene fusions are actually cellular congenital mesoblastic nephromas with hypocellular edematous areas at their edge which resemble the classic pattern. Recurrent intragenic internal tandem duplications of the *EGFR* kinase domain have been identified in most (approximately two thirds) classic and mixed congenital mesoblastic nephromas, but only rarely in cases diagnosed as cellular congenital mesoblastic nephroma (2 of 20 cases): the morphology of the latter was not illustrated in this study (61). Hence, mixed congenital mesoblastic nephroma is more closely linked genetically to the classic than the cellular subtype. While classic congenital mesoblastic nephromas are typically diploid, cellular congenital mesoblastic nephromas frequently demonstrate aneuploidy of chromosomes 11, 8, and 17 (54,57,62).

ETV6 is an ETS transcription factor previously implicated in translocations in pediatric B-cell acute lymphoblastic leukemia. *NTRK3* is a tyrosine kinase receptor that responds to extracellular signals. The *ETV6-NTRK3* fusion product is a constitutively active tyrosine kinase which promotes cellular growth via multiple downstream pathways (63). The identical gene fusion gene is characteristic of several epithelial neoplasms, including secretory carcinoma of the breast and mammary analog secretory carcinoma of the salivary gland. A few cases of cellular congenital mesoblastic nephroma have demonstrated a variant *EML4-NTRK3* gene fusion (64). Given the expanded genetic spectrum recently described in infantile fibrosarcoma of soft tissue (including *NTRK1, NTRK2, BRAF, RET,* and *MET* fusions), it seems likely that the genetic spectrum of cellular congenital mesoblastic nephroma will likewise expand.

Differential Diagnosis. The four neoplasms most likely to be confused with congenital mesoblastic nephroma in the infantile kidney are nephroblastoma, metanephric stromal tumor, clear cell sarcoma of the kidney (Table 1-15), and rhabdoid tumor. Because most congenital mesoblastic nephromas are managed by resection alone and the latter two entities are treated with aggressive and potentially toxic chemotherapy and radiation therapy regimens, the establishment of a correct diagnosis has tremendous clinical implications. Only nephroblastoma is considered in detail here because the differential approaches to metanephric stromal tumor, clear cell sarcoma of the kidney, and rhabdoid tumor are discussed in their respective sections. The characteristic molecular and immunohistochemical markers of the latter three neoplasms are not found in congenital mesoblastic nephroma. Specifically, the *BRAF* V600E mutation found in metanephric stromal tumor, the *BCOR* internal tandem duplication and strong diffuse nuclear BCOR immunoreactivity found in clear cell sarcoma, and *INI1* loss found in rhabdoid tumor are not found in congenital mesoblastic nephroma.

Nephroblastoma. Fewer than 2 percent of untreated nephroblastoma cases are composed predominantly of stromal cells (27). In most of these, the presence of immature or mature skeletal muscle readily excludes the diagnosis of congenital mesoblastic nephroma. Conversely, embryonal metaplastic changes in nephrons surrounded by congenital mesoblastic nephroma cells are sometimes misinterpreted as tubular or papillary elements in a nephroblastoma.

The most common errors in interpretation involve specimens removed after chemotherapy. Treatment often ablates the embryonal proliferating elements of a nephroblastoma but tends to spare stromal cells. The resultant appearance can readily be confused with congenital mesoblastic nephroma in some specimens. The following features are helpful in the differential diagnosis: 1) bilaterality, the presence of nephrogenic rests, or both strongly favors nephroblastoma; 2) an interdigitating, irregular border favors congenital mesoblastic nephroma; cellular congenital mesoblastic nephroma often has a sharp, pushing border, similar to that of most nephroblastomas; 3) blastemal foci do not occur in congenital mesoblastic nephroma, and skeletal muscle is never seen. Nodules of entrapped cartilage and squamous pearls may occur in congenital mesoblastic nephroma and should not be taken as evidence of nephroblastoma; and 4) nephroblastoma lacks the *ETV6-NTRK3* gene fusion of cellular congenital mesoblastic nephroma.

Treatment and Prognosis. Most congenital mesoblastic nephromas present as localized neoplasms. When completely excised, the prognosis is excellent. Only 5 percent of patients develop recurrence, which is mainly related to the completeness of resection, so the initial use of adjuvant therapy is not usually recommended unless there is known gross residual tumor following surgery.

A critical issue in evaluating nephrectomy specimens containing congenital mesoblastic nephroma is to establish whether the lesion was completely resected. As noted above, this often is impossible to establish with certainty. For this reason, in the majority of cases, close follow-up by imaging studies is recommended. The duration of intensive follow-up can be brief (29 of 31 relapsed cases recurred within 1 year of nephrectomy [J. Bruce Beckwith, unpublished observations, 2000]). Therefore, these patients typically are followed by monthly abdominal ultrasonography for 1 year, and can be presumed to be cured if there is no recurrence in that time (65).

Children with cellular type congenital mesoblastic nephroma, of age 3 months or older, or with stage III disease are more likely to relapse (66). Two thirds of recurrences are local; the remaining one third are distant metastases.

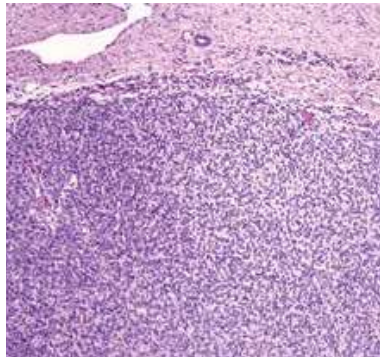


Figure 1-77

CONGENITAL MESOBLASTIC NEPHROMA, CELLULAR TYPE

This is a rare liver metastasis. Benign bile ducts are seen at the top.

The lung is the most common metastatic site, and a few cases of brain and liver metastases of cellular congenital mesoblastic nephroma have been reported (fig. 1-77) (67). Although relapses usually are highly responsive to adjuvant therapy (68,69), some are resistant, and complete surgical removal of recurrent disease is advisable whenever possible. Only rare tumor-related deaths have been reported (66,67,70,71). These are almost equally divided between disease-related and treatment- related causes. The latter often occur in newborns, reflecting the challenges of managing such frequently large neoplasms in very small patients.

CLEAR CELL SARCOMA OF THE KIDNEY

Definition. *Clear cell sarcoma of the kidney* is an uncommon renal sarcoma of uncertain histogenesis occurring in children that is characterized by nests of undifferentiated neoplastic cells associated with extracellular matrix supported by a branching vascular network (72–74). The term *bone metastasizing renal tumor of childhood* also has been used for this neoplasm (75–77).

General and Clinical Features. While the term clear cell sarcoma is also used for an unrelated soft tissue sarcoma showing melanocytic

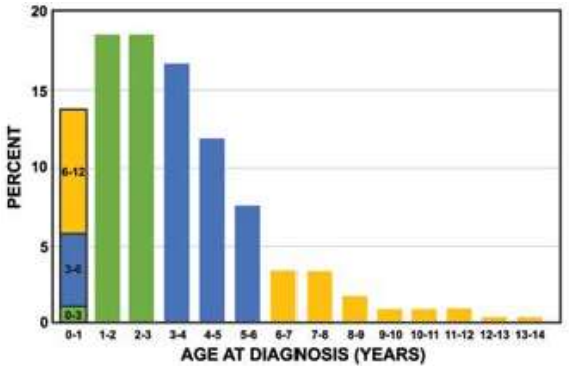


Figure 1-78

CLEAR CELL SARCOMA OF THE KIDNEY

Age distribution of 334 cases from the National Wilms Tumor Study Pathology Center.

Table 1-16

CLEAR CELL SARCOMA OF THE KIDNEY: KEY FEATURES

Mean age = 2 years
Entrapment of single native renal tubules at the tumor periphery
Branching capillary vasculature
Fine dispersed chromatin
Strong diffuse nuclear labeling for BCOR by immunohistochemistry
Absence of immunoreactivity for cytokeratin, desmin, CD34, S-100 protein
Unusual sites of metastasis (bone, brain, soft tissue)
Long interval to metastasis

differentiation, the term is used here to refer to the renal neoplasm. Clear cell sarcoma comprises approximately 3 percent of malignant renal tumors in childhood (Table 1-16) (78). There is no association with nephroblastoma-related syndromes or nephrogenic rests.

The male to female ratio is 2 to 1. The mean age at diagnosis is 36 months. Clear cell sarcoma is rarely diagnosed in the first 6 months of life but its incidence increases rapidly thereafter, peaking in the second and third years. The incidence decreases rapidly thereafter, but occasional cases are observed in adolescents and young adults (fig. 1-78). There is no known geographic or racial predisposition. Occasional extrarenal cases have been reported, and the concept of "extrarenal clear cell sarcoma" is now supported by the shared genetic alterations with clear cell sarcoma of kidney that these cases have shown (see below).

Clear cell sarcoma has distinct clinical manifestations. It usually has a slow growth rate, and a few tumors present with disseminated disease. In a comprehensive National Wilms Tumor Study (NWTS) report of 351 cases, 25 percent presented with stage I disease, 37 percent presented with stage II disease, 34 percent presented with stage III disease, and only 5 percent presented with hematogenous metastases (78). However, clear cell sarcoma frequently permeates renal lymphatics, and perirenal lymph node metastases are present in almost 30 percent of cases at diagnosis. The distribution and timing of metastases are also distinctive (see Prognosis). Importantly, the prognosis has been improved substantially by the addition of doxorubicin (adriamycin) to the therapeutic regimen (78), so the establishment of a correct diagnosis has great clinical significance.

Gross Findings. Clear cell sarcomas are typically large (mean diameter, 11 cm) and almost always unicentric. The median weight is 500 to 600 g. The tumors are not encapsulated but circumscribed, tan, soft, and mucoid (fig. 1-79). The color varies, but a glistening, gelatinous surface is often seen. Cysts are almost always present and rarely are prominent enough to suggest cystic nephroma on gross examination or imaging studies. There are no known precursor lesions.

Microscopic Findings. Under low magnification, most clear cell sarcomas appear monomorphous, without the prominent lobulation of nephroblastoma. The classic pattern of clear cell sarcoma of kidney is characterized by cords or nests of neoplastic cells separated by regularly spaced, arborizing fibrovascular septa (fig. 1-80A) (78). The septa may be thin, regularly branching "chicken-wire" capillaries, or thickened sheaths of fibroblastic cells surrounding a central capillary (fig. 1-80B). These fibrovascular septa subdivide the tumor into a conspicuous pattern of cords or nests, averaging 6 to 10 cells in width, and are composed of polygonal cells that usually lack distinct cytoplasmic borders (fig. 1-80C).

The cord cells may be polygonal or spindle shaped, and are loosely separated by extracellular myxoid material that mimics clear cytoplasm. The nuclei are round to oval, have fine chromatin, and lack prominent nucleoli (fig. 1-81). The cord cells are less densely packed than those of blastema in nephroblastoma, and overlapping nuclei are less frequent. In well-fixed specimens, the fine nuclear chromatin pattern is the most helpful clue to the diagnosis, but this feature can be influenced markedly by fixation. Delayed or inadequate fixation may cause clumping of chromatin in clear cell sarcoma, or some fixatives may make the chromatin of nephroblastoma appear finely granular. Mitotic figures are variable in number but are usually less numerous than those in nephroblastoma.

The cytoplasm of the cord cells usually lacks distinct borders, and as noted above, encloses vacuoles of extracellular mucopolysaccharide (hyaluronic acid), which are a distinctive and prominent feature of most clear cell sarcomas and contribute to their usually pale appearance on stained slides. These vacuoles may appear empty or contain blue-stained granular material, depending on the fixative and staining technique used. The name "clear cell sarcoma" can be misleading because the cytoplasm of the cord cells is pale rather than clear and some clear cell sarcomas contain cells with eosinophilic, sharply demarcated cytoplasm reminiscent of the cytoplasm of rhabdoid tumors. These cells are present either focally or diffusely, and bring a diagnosis of rhabdoid tumor of the kidney to mind, although their uniform, open chromatin is distinct from the vesicular chromatin and prominent nucleoli of rhabdoid tumor.

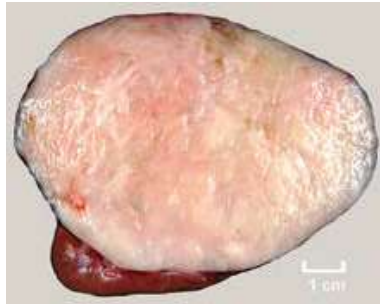


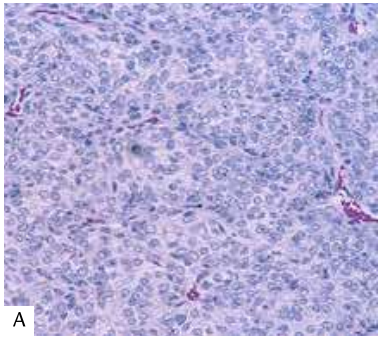
Figure 1-79

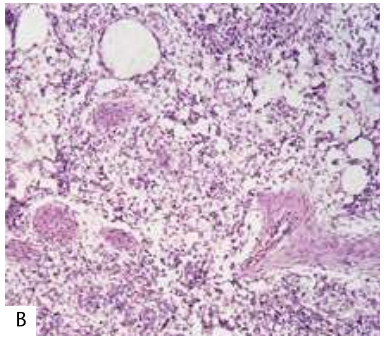
CLEAR CELL SARCOMA OF THE KIDNEY

Clear cell sarcomas of the kidney are homogeneous, mucoid, and often irregular in contour. The tumor-kidney junction appears sharply defined grossly.

While clear cell sarcomas grossly appear circumscribed, they typically have subtly infiltrative borders, entrapping and isolating components of nephrons (fig. 1-82). This pattern distinguishes clear cell sarcoma from most other renal neoplasms of children, which are either widely invasive (like rhabdoid tumor and diffuse blastemal nephroblastoma) or encapsulated (like most other nephroblastomas). The entrapped tubules are usually confined to the peripheral 2 to 3 cm of the tumor. The entrapped epithelium commonly shows embryonal metaplastic changes similar to those in congenital mesoblastic nephroma, and the resultant basophilic epithelium invites confusion with nephroblastoma (fig. 1-83). Dilatation of these entrapped tubules produces intratumoral cysts that may mimic cystic nephroma (fig. 1-84).

Fortunately, the classic pattern of clear cell sarcoma predominates in most specimens and is present at least focally in more than 90 percent of tumors. However, clear cell sarcoma may adopt any of a large number of variant histopathologic patterns, presenting alterations that mimic other neoplasms to a sometimes striking degree (78). The pathologist unaware of these





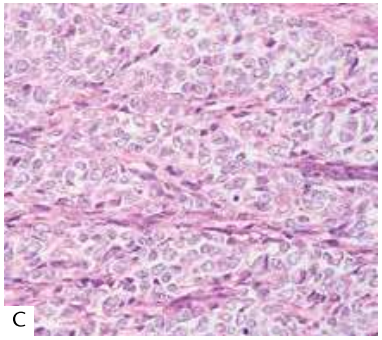


Figure 1-80

CLEAR CELL SARCOMA OF THE KIDNEY

A: In the classic pattern, cell cords are demarcated by delicate, regularly spaced, branching capillary septa.

B: Occasionally, the perivascular stroma becomes prominent, creating "cellular septa." These septal cells are likely non-neoplastic.

C: The cord cells have minimal cytoplasm, but are separated by clear spaces which simulate clear cytoplasm. The nuclei have open, finely dispersed chromatin with occasional inclusions.

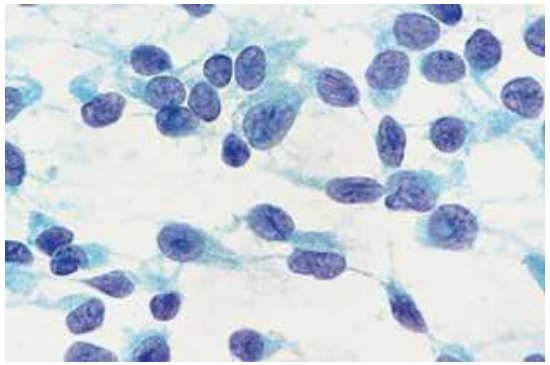


Figure 1-81

CLEAR CELL SARCOMA OF THE KIDNEY

Fine-needle aspiration cytology demonstrates nuclei with fine, evenly dispersed chromatin and occasional nuclear grooves.

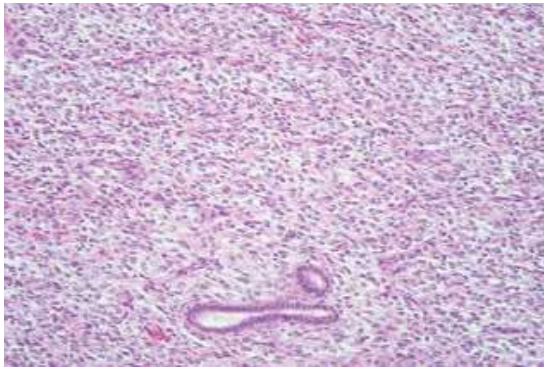
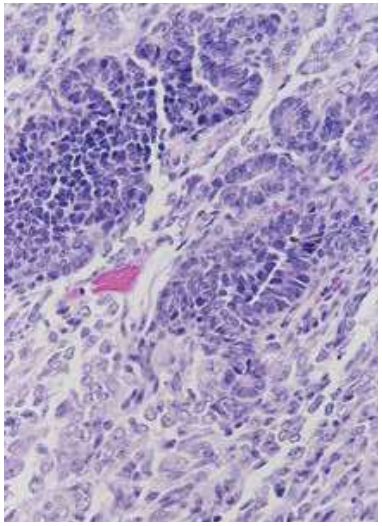


Figure 1-82

CLEAR CELL SARCOMA OF THE KIDNEY

Clear cell sarcoma of the kidney characteristically entraps single tubules at its interface with the kidney.



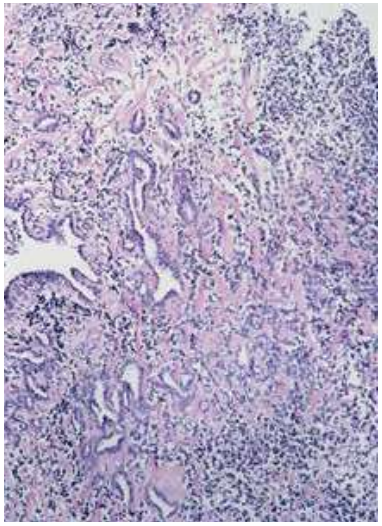


Figure 1-83

CLEAR CELL SARCOMA OF THE KIDNEY

Left: Entrapped renal tubules frequently demonstrate embryonal hyperplasia, which, especially when nodular, closely simulates biphasic nephroblastoma.

Right: Florid embryonal hyperplasia of entrapped tubules simulates nephroblastoma. The collagen within the lesion is uncommon in untreated nephroblastoma.