Educational Case

Educational Case: Wilms Tumor

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Alison R. Huppmann, MD[1]

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, organ system pathology, kidney, renal neoplasia, Wilms tumor, pediatric, syndrome

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Primary Objective

Objective UTK1.4: Wilms Tumor. Describe the clinical and pathologic features and molecular basis for Wilms tumor and list the histologic features that are important to recognize in determining prognosis, and the etiology of Wilms tumor as part of different syndromes.

Competency 2: Organ System Pathology; Topic UTK: Kidney; Learning Goal 1: Renal Neoplasia.

Patient Presentation

A 2-year-old boy presents to his pediatrician after his mother noticed a "lump in his belly." Further questioning reveals only that the patient has seemed slightly more tired lately. He has a history of a urinary tract malformation that required surgical repair. Family history is negative for malignancy or major medical problems. Physical examination reveals a blood pressure of 142/94 mm Hg with other vital signs within normal limits. A large mass is palpable in the abdomen and appears to be centered on the right side.

Diagnostic Findings

An abdominal ultrasound shows a solid mass in the right abdomen. A computed tomography (CT) scan discloses a mass arising from the right kidney (Figure 1). A nephrectomy is performed.

Questions/Discussion Points

Which Entities May Present as an Abdominal Mass in a Child? Include Both Neoplastic and Nonneoplastic Lesions

For abdominal masses occurring at birth or within the first few years of life, congenital anomalies are a strong consideration, including gastrointestinal tract duplications, cysts arising from the omentum or mesentery, cysts of the hepatobiliary system, intussusception, and genitourinary tract anomalies such as polycystic or hydronephrotic kidneys or an enlarged bladder. Splenomegaly or hepatomegaly, for any reason, may present as a mass. If trauma is an antecedent factor, the cause may be a hematoma or pancreatic pseudocyst. An intra-abdominal abscess, most commonly arising from the appendix, is another benign cause. Malignant tumors can also occur in the abdomen, including neuroblastoma, Wilms tumor, hepatoblastoma, germ

[1] Department of Pathology, School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Corresponding Author:
Alison R. Huppmann, Department of Pathology, School of Medicine, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814, USA.
Email: alison.huppmann@usuhs.edu

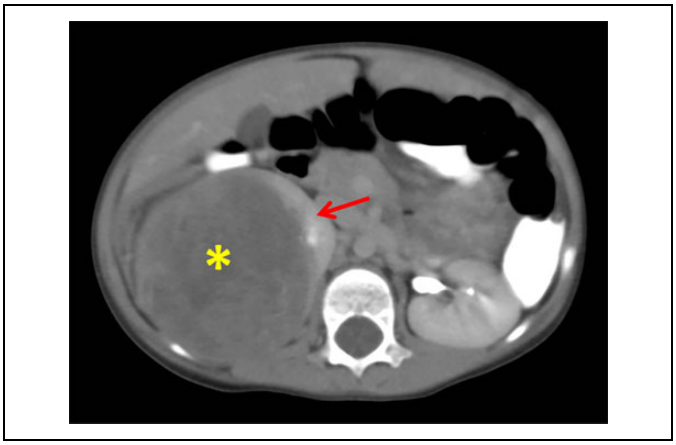

Figure 1. A computed tomography (CT) scan shows a large mass (*) on the right side with the remaining kidney (arrow) showing the "claw sign" around the mass, indicating that is likely of renal origin.

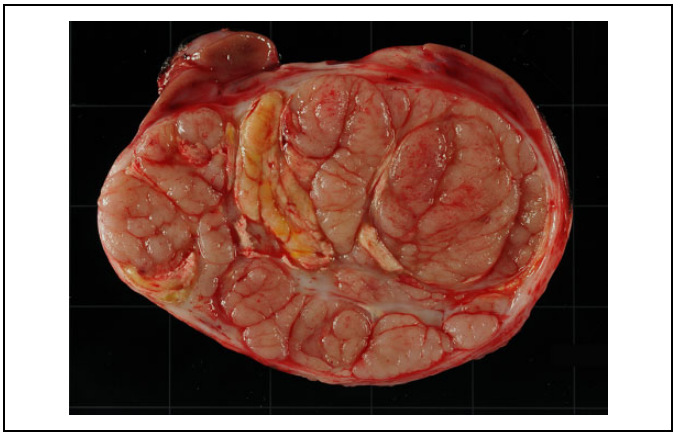

Figure 2. Grossly, a large, tan, well-circumscribed, encapsulated mass has replaced much of the normal renal parenchyma. Yellow discoloration indicates areas of necrosis.

cell tumors, sarcomas (eg, rhabdomyosarcoma), and rarely lymphomas.[1]

Describe the Gross and Histologic Features in Figures 2-4. Based on the Clinical and Pathologic Features, What Is Your Diagnosis?

Grossly, a large, tan, fleshy, well-circumscribed mass replaces most of the renal parenchyma (Figure 2). Foci of yellow discoloration indicate necrosis. A capsule surrounds the periphery of the mass. Areas of hemorrhage and/or cystic change can be seen in some cases. The low-power histologic image (Figure 3) demonstrates a variable appearance due to several different components of the tumor. A higher power view (Figure 4) allows closer examination of these varied elements, showing a mixture of immature tubules, small round blue cells, and spindled cells. These findings are consistent with a diagnosis of Wilms tumor (nephroblastoma).

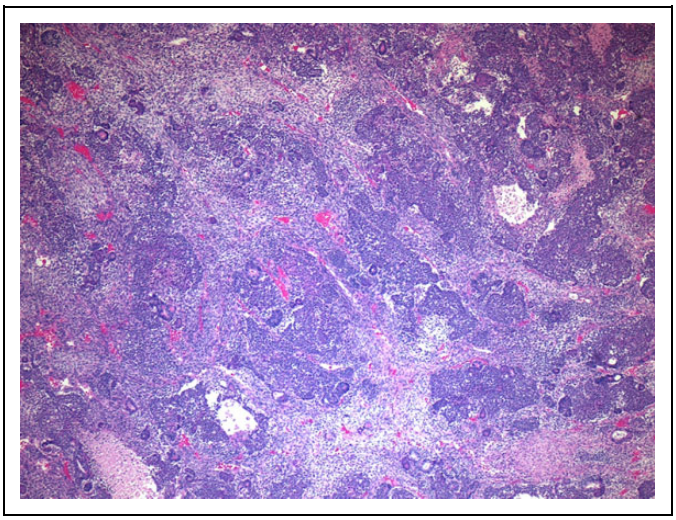

Figure 3. On low power magnification of the mass, the histology shows a variable appearance due to the different elements composing the tumor (hematoxylin and eosin, ×40).

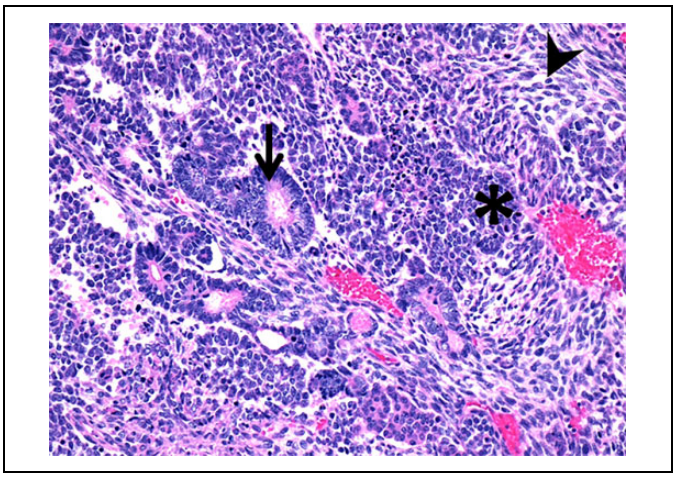

Figure 4. At intermediate magnification, primitive tubules (arrow), small round blue cells (*), and spindled cells (arrowhead) represent epithelial, blastemal, and stromal components, respectively (hematoxylin and eosin, ×200).

Like some other pediatric tumors, the histology of Wilms tumor appears similar to primitive (embryonic or fetal) elements that would have been present in the tissue of origination, in this case the kidney (Figure 5). A classic Wilms tumor is triphasic, with epithelial, blastemal, and stromal elements; although any one of these 3 may predominate in a given tumor. Immature tubules and glomeruli compose the epithelial areas. The blastemal cells are undifferentiated-appearing small blue cells. Stromal cells are usually spindled with a fibrotic or myxoid background, and heterologous differentiation (skeletal muscle, cartilage, osteoid, etc) can be found in some cases (not seen in these images).[2]

Wilms tumor is the most common primary renal malignancy of childhood.[2] Other primary renal tumors of childhood include

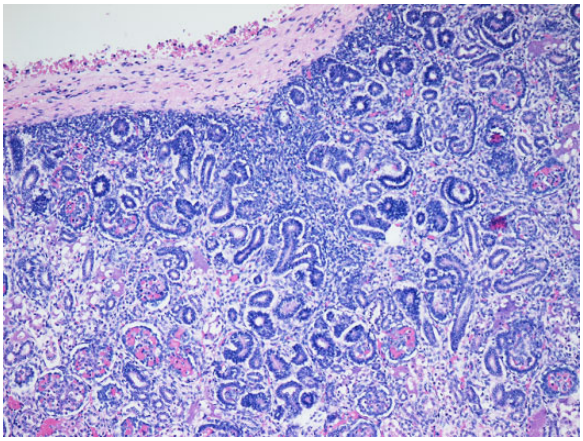

Figure 5. This is the histologic appearance of fetal renal cortex at 19 weeks' gestation. Note the nephrogenic zone in the subcapsular area and its histologic similarity to Wilms tumor, with primitive glomeruli, tubules, and blastema (hematoxylin and eosin, ×100). The nephrogenic zone should disappear by approximately 36 weeks' gestation.

mesoblastic nephroma, clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, and, in adolescents, renal cell carcinoma. These tumors do not contain the triphasic elements seen in Wilms tumors.

What Is the Typical Clinical Presentation of a Wilms Tumor?

Wilms tumor most commonly occurs in young children between age 2 and 5. However, older children and even adults can be affected. The most common presentation is an abdominal mass. These are often identified by a caregiver while bathing or changing the child's clothes or by a physician on routine physical examination. Other frequent signs and symptoms include hypertension, abdominal pain, fever, painless hematuria, and anemia.[3]

What Other Tumors Are Included in the Category of "Small Round Blue Cells Tumors"? How Are These Differentiated?

Small round blue cell tumors are those composed of cells with scant cytoplasm, so that the tumor appears "blue" (basophilic) from low power since the nuclei dominate the histology. Tumors commonly included in this group are leukemia/lymphoma, neuroblastoma, Wilms tumor, rhabdomyosarcoma, Ewing sarcoma family of tumors, desmoplastic small round cell tumor, rhabdoid tumor, and other undifferentiated types of sarcoma. Note that most of these tumor types are more common in children. Many of the small round blue cell tumors of childhood show histological features that permit a preliminary diagnosis. Panels of immunohistochemical stains and genetic or molecular testing are useful to confirm the findings.

What Are Nephrogenic Rests? What Is Their Significance?

Nephrogenic rests are nonencapsulated areas of persistent immature renal tissue with histologic features that can resemble Wilms tumor. These rests usually regress or differentiate, but they can become malignant if they persist. Evidence supporting this theory includes shared genetic alterations with rests and tumor in the same patient.[2] Although seen in 1% of the general population,[3] nephrogenic rests are identified in the adjacent renal parenchyma of up to 40% of patients with unilateral tumors and almost 100% of bilateral tumors. These rests are important to identify, as they imply an increased risk of Wilms tumor in the contralateral kidney, necessitating close monitoring of the patient.[2]

Which Patient Characteristics Might Lead You to Suspect an Associated Syndrome in a Pediatric Patient With Cancer? Which Congenital Syndromes Are Most Often Associated With Wilms Tumor?

The possibility of a syndrome should be considered in any pediatric oncology patient with a personal or family history of malformation(s), personal or family history of malignancy, early onset of cancer, certain physical characteristics, or rare forms of cancer. Approximately 10% of Wilms tumors occur in patients with congenital syndromes. Those most commonly associated are WAGR syndrome (*W*ilms tumor, *a*niridia, *g*enital anomalies, mental *r*etardation), Denys-Drash syndrome (renal mesangial sclerosis, early-onset renal failure, gonadal dysgenesis), and Beckwith-Wiedemann syndrome (hemihypertrophy, organomegaly, macroglossia, and omphalocele). A large number of other syndromes are less commonly associated.[2]

Describe Some of the Common Genetic Changes Associated With Wilms Tumor

Genetic mutation(s) have been identified in one-third of Wilms tumors as yet. Some of these have been found due to their association with the congenital syndromes that convey an increased risk of Wilms tumor. Both WAGR and Denys-Drash syndromes are associated with mutations in the *WT1* gene, although due to a deletion in WAGR and a missense mutation in Denys-Drash. *WT1* is a tumor suppressor gene and encodes for a transcription factor that plays a critical role in development of the kidneys and gonads. The homozygous *WT1* mutations detected in Wilms tumors lead to loss of function.[2]

Beckwith-Wiedemann syndrome is associated with alterations in chromosome 11p15.5. One of the genes in this region, *IGF2*, is normally imprinted, with expression only by the paternal allele. Either loss of imprinting or uniparental disomy of *IGF2* has been identified in some Wilms tumors.[2]

CTNNB1 encodes for β-catenin, a key regulator of the Wnt signaling pathway. Mutations in *CTNNB1* are identified in 10% to 15% of Wilms tumors. Another gene associated with the

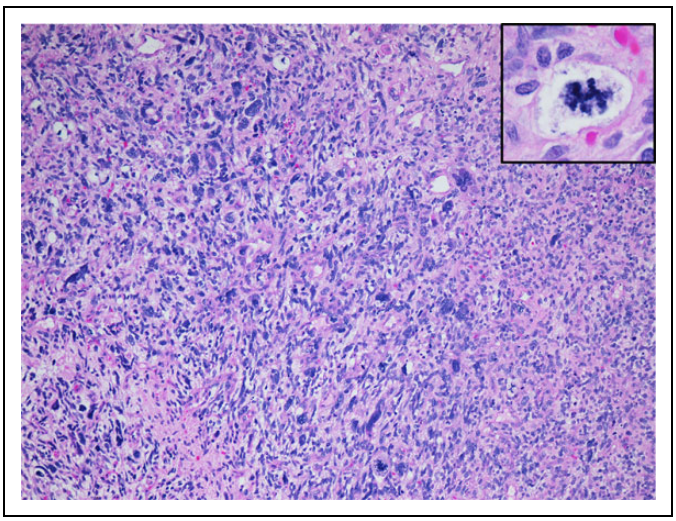

Figure 6. This tumor contains scattered cells with hyperchromatic nuclei that are much larger than the other nuclei. The inset shows an atypical mitotic figure. These findings indicate anaplasia (hematoxylin and eosin, ×100; inset, ×1000).

same pathway, *WTX*, is mutated in some tumors; *TP53* mutations are even less frequent. Many other less frequent genetic mutations have been identified, either alone or in combination with those previously discussed.[3]

What Histological Feature in Wilms Tumor Is Considered to be Unfavorable?

The feature in Wilms tumor indicative of unfavorable histology is anaplasia. This is shown in Figure 6. Anaplasia in Wilms tumor is defined as the presence of cells with large hyperchromatic nuclei (generally at least 3 times the size of adjacent nonanaplastic nuclei) and the presence of abnormal, polyploid mitotic figures. It is seen in 5% to 10% of Wilms tumors. As a diffuse finding, anaplasia is associated with resistance to chemotherapy and conveys a poorer prognosis in advanced-stage disease. It is linked to *TP53* mutations.[4]

Where Is Wilms Tumor Most Likely to Spread?

Renal vein extension is common. Noncontiguous spread goes to the regional lymph nodes, with the lungs being the most common site of distant metastasis.

What Other Factors Affect Prognosis in Wilms Tumor?

Tumor histology is possibly the most critical factor affecting prognosis, but other aspects considered include tumor stage, patient age, loss of heterozygosity (LOH) for chromosomes 1p and 16q, tumor weight, and completeness of lung nodule response. Briefly, staging for Wilms tumors is as follows: stage I—tumor confined to the kidney and removed completely by surgery; stage II—tumor extends beyond the kidney but is completely removed by surgery; stage III—tumor remains in the patient after surgery but is confined to the abdomen; stage IV—hematogenous metastases to lungs, liver, lymph nodes outside the abdomen, and so on; stage V—bilateral tumors at diagnosis. Notably, if a biopsy is performed prior to resection, the patient is automatically at least Stage III, which is why biopsy is not often utilized for pediatric renal tumors.[4]

Current treatment includes surgery and chemotherapy with or without radiation. The last 50 years have shown a dramatic improvement in prognosis for patients with Wilms tumor, with a current cure rate of approximately 90%.[4]

Teaching Points

- Wilms tumor is the most common primary renal tumor of childhood, most commonly presenting as an abdominal mass in a child 2 to 5 years of age.
- Many benign and malignant conditions can present as an abdominal mass in a child, necessitating a complete evaluation of the patient to arrive at the correct diagnosis.
- Genetic changes involved in the pathogenesis of Wilms tumor include the *WT1* gene and chromosome 11p15.5. These were partly identified through their association with some of the congenital syndromes with an increased risk of Wilms tumor, WAGR, Denys-Drash, and Beckwith-Wiedemann syndromes.
- An associated congenital syndrome should be suspected in a pediatric oncology patient with a personal or family history of a malformation or malignancy.
- A classic Wilms tumor has triphasic histology, including epithelial, blastemal, and stromal elements. Nephrogenic rests are presumed precursors to Wilms tumor and can have similar histologic features, although they are not encapsulated.
- Small round blue cells tumors have a similar histologic appearance of small cells with scant cytoplasm. Many of these tumors occur in childhood and include Wilms tumor, neuroblastoma, leukemia/lymphoma, rhabdomyosarcoma, and Ewing sarcoma family of tumors.
- Histology is a key predictor of prognosis in Wilms tumor, as anaplasia is associated with a less favorable prognosis. Other prognostic markers include age, stage, LOH 1p and 16q, tumor weight, and responsiveness of lung metastases.

Author's Note

The opinions expressed herein are those of the author and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

Declaration of Conflicting Interests

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