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Educational Case: Wilms Tumor (Nephroblastoma)

Taylor E. Anderson, BA[1] and Richard M. Conran, MD, PhD, JD[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, nephroblastoma, abdominal mass, pediatric tumors

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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 3-year-old male presents to the clinic with his mother who has noticed a rapidly growing mass in the left side of his abdomen. She has also noticed a pink tinge to his urine and noted that he often cries with urination. On physical examination, the physician palpated a large left-sided abdominal mass with smooth, regular margins that did not cross the midline. The rest of the physical examination was unremarkable. Ultrasound and contrast-enhanced computed tomography (CT) scans of the abdomen were ordered.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis for an Abdominal Mass in a Young Child?

The differential diagnosis for an abdominal mass in a young child consists of disorders of renal origin (neoplastic, nonneoplastic), cysts of other abdominal organs (mesenteric, omental, choledochal), other neoplasms (neuroblastoma, teratoma, hepatoblastoma), or congenital (developmental) abnormalities.[1]

Diagnostic Findings, Part 2

Imaging

Ultrasound revealed an 8 × 7 cm well-defined mass of heterogeneous echogenicity arising from the left kidney. Heterogeneity is due to hemorrhage and necrosis. On CT scan, a large mass with low-density areas signifying tumor necrosis was seen. There was no evidence of nodal or hepatic metastasis. The right kidney was unremarkable.

Pathologic Examination

The left kidney was resected (Figure 1). On gross examination, a lobulated tan mass with surrounding pseudocapsule is visualized arising from the left kidney. It appears as a heterogenous

[1] Eastern Virginia Medical School, Norfolk, VA, USA

Corresponding Author:
Richard M. Conran, Eastern Virginia Medical School, 700 West Olney, Norfolk, VA 23501, USA.
Email: conranrm@evms.edu

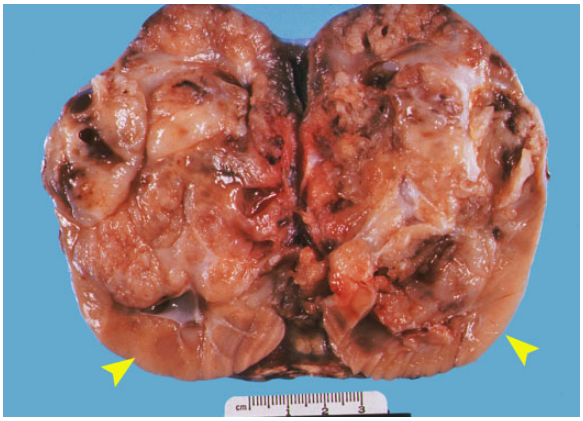

Figure 1. Kidney sectioned in half showing a hemorrhagic tan-white 8 × 7 cm necrotic mass compressing the non-neoplastic renal parenchyma (arrowheads).

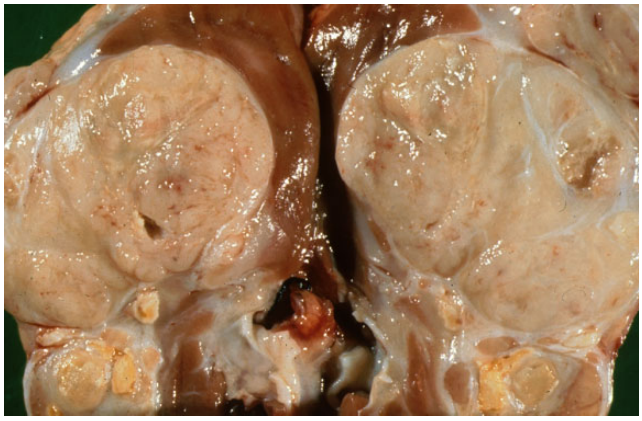

Figure 3. The bisected kidney demonstrates a large, tan-white, bulging, well-demarcated tumor compressing the normal renal parenchyma.

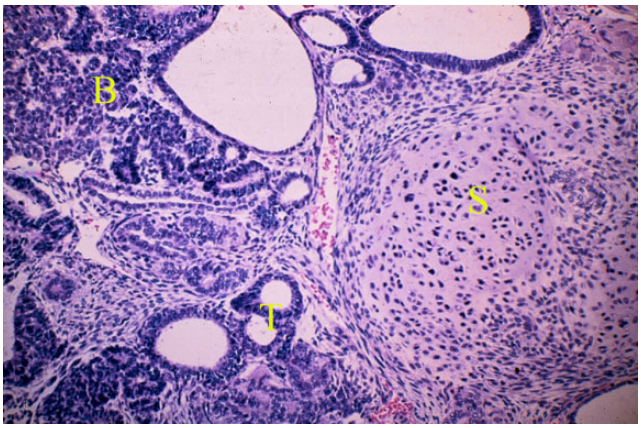

Figure 2. Triphasic tumor composed of blastema (B), epithelial elements (tubules) (T), and stroma (S). H&E, Intermediate power.

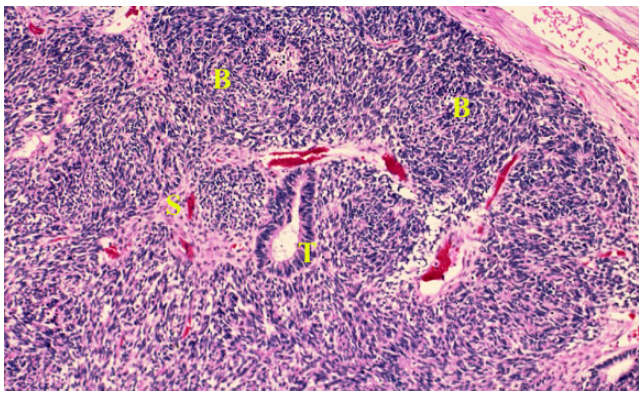

Figure 4. Blastema-predominant Wilms tumor composed of small round blue cells (B) intermixed with single tubule (T) and stromal elements (S). H&E, Intermediate power.

mass with prominent foci of necrosis and hemorrhage. Tissue submitted for histological examination demonstrates a mixed pattern of blastemal, stromal, and epithelial elements (Figure 2).

Questions/Discussion Points, Part 2

What Is the Diagnosis Based on the Clinical, Imaging, Gross and Histological Findings?

The clinical (left-sided abdominal mass), imaging (8 × 7 cm heterogenous echogenic mass on ultrasonography), gross (lobulated tan heterogenous mass), and histological findings (mixed pattern of blastemal, stromal, and epithelial elements) are consistent with a diagnosis of Wilms tumor (WT; nephroblastoma).

Describe the Gross and Microscopic Pathologic Features of Nephroblastoma

Grossly, the mass may appear as a large, bulging, tan-white lobulated, homogenous mass that is sharply demarcated from the renal parenchyma (Figure 3) or as a heterogeneous mass with necrosis and hemorrhage, as in this case (Figure 1).[2] Wilms tumor typically occurs unilaterally, but in 5% to 10% of cases the malignancy appears bilaterally, either simultaneously or one after the other. Microscopically, the classic WT is a combination of blastemal, stromal, and epithelial elements (mixed tumor; Figure 2). Neoplasms containing all elements are commonly referred to as triphasic tumors. When one component consists of more than two-thirds of a tumor, the term monophasic tumor is used. The triphasic tumor is the most frequent pattern followed by the blastema-predominant pattern (Figure 4). Blastemal cells are the least differentiated and consist of primitive small round blue cells. The epithelial component ranges from primitive rosette-like structures to tubules or glomerular-like structures. The stromal component appears as densely packed undifferentiated mesenchymal cells interspersed with loose cellular myxoid regions or contain heterologous elements (skeletal muscle, cartilage, and bone).[3]

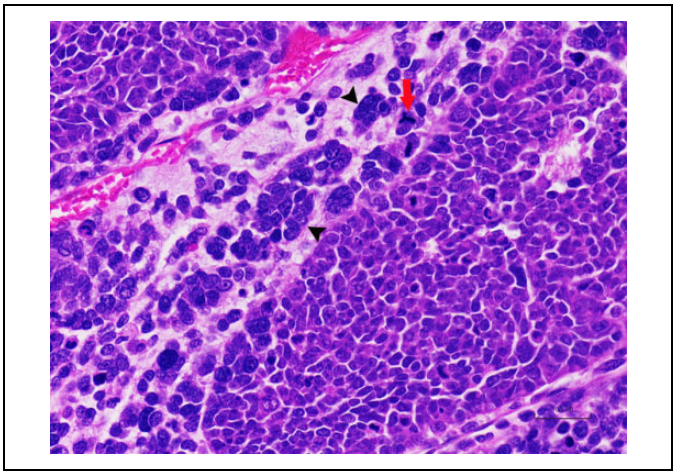

Figure 5. The large hyperchromatic cells (arrowheads) and atypical mitotic figure (red arrow) are demonstrative of anaplasia in a nephroblastoma. H&E, Intermediate power.

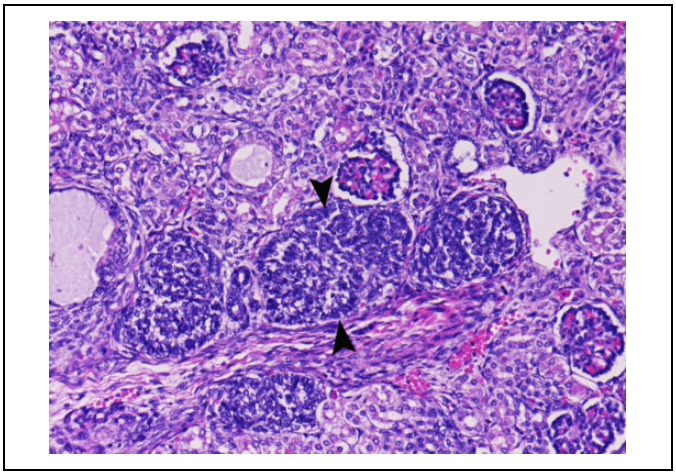

Figure 6. Nephrogenic rest. Persistent foci of embryonic cells (arrowheads) are present within the renal parenchyma. H&E, Intermediate power.

What Histological Finding Is Classified as Unfavorable Histology?

The presence of diffuse anaplastic histology, observed in approximately 5% of WTs, would correlate with a poor prognosis. Three features define anaplasia: prominent cytologic atypia (nuclear diameter greater than 3 times the size of the adjacent nuclei), hyperchromasia, and atypical mitotic figures (Figure 5). Anaplasia classified as "unfavorable histology" correlates with TP53 mutations and resistance to chemotherapy.[4]

What Is the Epidemiology of Wilms Tumor in the United States?

Wilms tumor has an incidence of 1 in 10 000 children in the United States.[4,5] It is the most prevalent primary renal tumor and the most common intra-abdominal solid tumor of childhood. Wilms tumor is the fourth most common malignancy in the pediatric population in the United States. Peak incidence is between ages 2 and 4 with 80% of cases presenting before age 5.[6]

Describe the Molecular and Developmental Abnormalities Associated With Wilms Tumor

Both inherited and sporadic forms of WT can arise. Mutation involving inactivation of the WT1 tumor suppressor gene locus on chromosome 11p13 often is a predisposing factor. Wilms tumor 1 protein normally functions as a transcriptional activator of genes that are involved in differentiation of renal and gonadal cells. It is a primary regulatory component during kidney development that governs the transition from mesenchymal cells to epithelial cells.[7]

Define "Nephrogenic Rests"

Nephrogenic rests (NRs) are abnormal areas of embryonic tissue that persist beyond 36 weeks of development and may be either perilobar or intralobar and are thought to be a precursor lesion for WT (Figure 6).[3,4] Nephrogenic rests are observed in approximately 25% to 40% of unilateral WT cases and 100% of bilateral WT cases. Perilobar NRs occur peripheral to the renal lobules and have been associated with the Beckwith-Wiedemann syndrome. Intralobar NRs are found within the central part of the lobule and have been associated with WAGR and Deny-Drash syndromes.[8]

What Syndromes Are Associated With Wilms Tumor?

Wilms tumors associated with syndromes account for approximately 10% of all cases.[4] WAGR syndrome is one such syndrome consisting of WT, aniridia, genital anomalies (cryptorchidism, hypospadias, etc), and mental retardation.[4,6] Approximately one-third of individuals with WAGR syndrome will develop WT over the course of their lifetime. This syndrome is characterized by germline deletion of chromosome 11p13 which carries the WT1 and PAX6 genes coding for WT and aniridia, respectively. Another syndrome increasing the risk of developing WT is Denys-Drash syndrome consisting of pseudohermaphroditism and progressive glomerulonephritis leading to renal failure. This syndrome is caused by altered DNA-binding properties of the zinc finger region of the WT1 protein due to a dominant negative missense mutation. Wilms tumor is seen in these patients only when there is biallelic inactivation of WT1. Beckwith-Wiedemann syndrome is another instance of increased risk of development of WT and occurs due to loss of function of the WT2 gene on chromosome 11p15. This syndrome is characterized by macroglossia, omphalocele, organomegaly, genitourinary anomalies, and increased risk of abdominal tumors. Genes present in the 11p15.5 region are normally subjected to imprinting, so only one of the 2 parental alleles are expressed. The phenotype and predisposition to tumorigenesis are specific to the type of imprinting abnormality that is seen in the affected individual. The insulin-like growth factor-2 gene expression has the

greatest correlation with tumor predisposition in Beckwith-Wiedemann syndrome.

What Other Neoplasms Are in the Differential?

Other renal tumors include congenital mesoblastic nephroma, clear-cell sarcoma, and rhabdoid tumor.[5,7] Other small round blue cell tumors of childhood that should be considered include neuroblastoma and primitive neuroectodermal tumor. Hepatoblastoma is another malignancy in the differential. Differential diagnosis is based on clinical and imaging findings. Diagnosis is based on pathologic features.

What Are Therapeutic Options After Diagnosis of Wilms Tumor?

Most patients can be cured of WT. Tumor staging is a surgical and pathological designation; most commonly the North American National Wilms Tumor Study Group staging system is used. In the United States, surgical resection is the first step in treatment and staging and will be followed by chemotherapy and radiotherapy if indicated.[7] Protocol in other countries involves primary treatment with chemotherapy to decrease the risk of intraoperative rupture and hemorrhage and to reduce the disease stage at the time of surgical resection. Stage I disease is limited to the kidney with the capsule intact and can be removed completely. Stage II disease indicates tumor has extended locally beyond the kidney capsule but is completely excised. Stage III WT is designated for tumors that cannot be completely excised. After surgery, there is residual nonhematogenous tumor that may include positive hilar or periaortic lymph nodes or positive margins at location of excision. Stage III also includes suspected peritoneal contamination following tumor rupture or surgical biopsy. Presence of distant tumor deposits such as lung, liver, or bone involvement qualifies as stage IV disease. Stage V WT is defined as bilateral renal tumors at the time of diagnosis. Each tumor is staged separately.[9]

Teaching Points

- An unidentified mass in an infant can be of renal (55%), gastrointestinal (15%), pelvic (15%), adrenal (10%), or hepatobiliary (5%) origin.
- Wilms tumor is the most common renal malignancy in children with an incidence of 1 in every 10 000 children.
- Wilms tumor is primarily a sporadic disease, but it can be associated with several congenital syndromes including WAGR syndrome, Denys-Drash syndrome, and Beckwith-Wiedemann syndrome.
- Diagnosis of WT requires histological confirmation, and staging is determined by the anatomic extent of the tumor.
- Therapeutic options at presentation, based on stage, consist primarily of surgical resection followed by adjuvant chemotherapy or radiation therapy in patients with more advanced disease.
- Diffuse anaplasia is an adverse prognostic feature in WT.

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Declaration of Conflicting Interests

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