**Neuroblastoma/Related Tumors and Renal Tumors**

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1. A 6-month-old boy presents with asymptomatic abdominal distension. Imaging reveals an adrenal mass without regional lymphatic spread. The patient undergoes adrenalectomy and complete resection of the tumor. No additional sites of tumor are noted during surgical exploration.

What are the pathologic features most likely to be seen for this patient?

A. Triphasic histologic pattern with epithelial, stromal, and blastemal/cellular component

B. Hyperchromatic cells with scan cytoplasm and rare mitoses intermixed with stromal Schwannian component

C. Atypical basophilic cells with numerous mitoses and a prominent starry-sky pattern

D. Primitive appearing basophilic round cells with cytoplasmic thick and thin filaments

**Explanation**

Neuroblastoma arises from sympathetic ganglion cells and is the most likely tumor to arise from the adrenal gland of an infant. Pathology consists of neuroblasts and Schwannian stroma, with individual cases evaluated based on the degree of neuroblastic differentiation and amount of stromal component. Tumors arising in infants can be less differentiated—hence the hyperchromatic small cells—but they still carry a favorable prognosis if there is no associated *MYCN* gene amplification within the tumor. Tumors with *MYCN* gene amplification usually have a higher mitotic index. Similarly, *MYC* gene overexpression occurs in Burkitt lymphoma, resulting in the characteristic undifferentiated lymphoblasts with high mitotic index and apoptosis that create the starry-sky appearance. Two other tumors with a histopathology consisting of small basophilic cells include Wilms tumor, with classic triphasic pattern histology of stroma, tubules, and cellular components, and rhabdomyosarcoma, in which rhabdoblastic filaments can sometimes be appreciated with the cytoplasm.

2. A toddler presents with secretory diarrhea, hypokalemia, and abdominal pain. Exam reveals abdominal distension and a questionable mass. Subsequent anatomical imaging demonstrates a retroperitoneal infiltrative soft tissue mass.

What is the most likely etiology of the patient’s diarrhea?

A. Neuroblastoma with diarrhea caused by infiltration of mesenteric vasculature

B. Neuroblastoma with diarrhea caused by tumor-related catecholamine secretion

C. Neuroblastoma with diarrhea caused by vasoactive intestinal peptide

D. Neuroblastoma with diarrhea caused by concurrent infectious gastroenteritis

**Explanation**

Secretory diarrhea is a rare syndrome associated with neuroblastoma, usually occurring in toddlers with retroperitoneal mass. The syndrome is caused by tumor secretion of vasoactive intestinal peptide (VIP). VIP acts on the intestinal epithelial cells via the blood circulation, causing excessive secretion of intestinal fluid, promoting pancreatic juice and bile secretion and exacerbating the loss of water and electrolytes. Although rare, neuroblastoma should be in the differential diagnosis for etiology of noninfectious severe secretory diarrhea.

3. A teenage girl presents with flank pain and hematuria. Imaging reveals a localized mass in the left kidney. Nephrectomy is undertaken with gross total resection of the mass. The pathology reveals renal cell carcinoma. Metastatic evaluation is negative for diseases outside the kidney.

What subsequent steps should be included in management?

A. Observation with serial imaging

B. Multiagent chemotherapy plus involved field radiotherapy

C. Radiotherapy

D. Immune modulation therapy or molecular targeted therapy with tyrosine kinase inhibition

**Explanation**

Survival after diagnosis of renal cell carcinoma is affected by the stage of disease at presentation and the completeness of resection at radical nephrectomy. Renal cell carcinoma is poorly responsive to chemotherapy and radiotherapy; therefore, these treatment modalities are rarely used. Survival for patients with nodal or distant metastatic disease is poor. Immune modulatory therapy, including IFN-γ or IL-2, or molecularly targeted therapy, which inhibits the mTOR pathway or angiogenic pathways, is used for patients with metastatic disease.

4. A-2-year-old boy presents to his pediatrician for evaluation of hematuria. On exam he is noted to have a palpable right flank mass. Ultrasound imaging and subsequent CT anatomical imaging confirm a large right renal mass without evidence of nodal or distant metastatic disease. The patient undergoes nephrectomy with complete tumor resection without tumor rupture. Pathology assessment confirms diagnosis of Wilms tumor with no anaplasia, no tumor extension beyond the renal capsule, and no nodal involvement. Multifocal nephroblastomatosis is noted in the remaining renal parenchyma.

Which of the following prognosis assessments should be provided to the family?

A. Patient will need chemotherapy and radiotherapy and has long-term risks for musculoskeletal changes and secondary malignancies.

B. Patient will need chemotherapy but no radiotherapy, and overall prognosis is excellent.

C. Patient will need only surgery, with excellent prognosis for cure.

D. Patient will need chemotherapy without radiotherapy but remains at risk for recurrence and will need prolonged surveillance for 8 to 10 years after diagnosis.

**Explanation**

Staging for Wilms tumor is related to completeness of resection, whether or not the tumor invades through the renal cortex or involves lymph nodes. This tumor is stage 1, as defined by its confinement to the kidney without capsular or sinus invasion and its negative lymph node pathology, with therapy consisting only of chemotherapy. The presence of nephroblastomatosis is associated with increased risk for recurrence locally or in the contralateral kidney and not always associated with a documented germline genetic predisposition for Wilms. The increased risk for recurrence mandates serial imaging for 8 to 10 years after diagnosis.

5. A 3-year-old girl presents with asymptomatic hematuria. Diagnostic evaluation reveals a right renal mass, with Doppler imaging confirming a thrombus in the inferior vena cava and extending superior to the hepatic veins. Liver function is normal. The presumptive diagnosis is Wilms tumor.

Which of the following next steps should the treating physician recommend?

A. Radical nephrectomy followed by initiation of chemotherapy and radiotherapy

B. Radical nephrectomy followed by initiation of chemotherapy

C. Biopsy followed by initiation of chemotherapy

D. Biopsy followed by initiation of radiotherapy

**Explanation**

Upfront radical nephrectomy with complete resection of Wilms tumor is standard approach for care in North America except in the following clinical scenarios: synchronous bilateral Wilms tumor or solitary kidney where preservation of renal function is of either immediate or long-term concern; extension of tumor thrombus in the inferior vena cava above the level of the hepatic veins, given the unlikely ability to completely resect and concern for resultant pulmonary tumor emboli; tumor deemed not resectable because of the involvement of contiguous structures, whereby the only means of removing the kidney tumor requires removal of the other structures; and pulmonary compromise caused by extensive pulmonary metastases. Biopsy is recommended in North America to confirm the diagnosis of Wilms tumor; however, upfront initiation of chemotherapy without biopsy is recommended in Europe. Radiotherapy is delayed until after resection of the tumor.

6. A 14-month-old boy presents to the emergency department for evaluation with acute onset of ataxia without current or recent preceding symptoms of viral infection. Your exam reveals an afebrile child with normal blood pressure and heart rate. The patient is agitated but can follow commands and is oriented to person. Neurologic exam reveals opsoclonus and ataxia without focal cranial nerve deficits or focal weakness. Cranial CT scan, MRI, serum electrolytes, and peripheral blood counts are normal.

What is the most likely diagnosis?

A. Posterior fossa brain tumor

B. Seizure disorder

C. Neuroblastoma

D. Leukemia with CNS involvement

**Explanation**

The patient presents with opsoclonus myoclonus ataxia syndrome (OMAS), most commonly seen in children as a postviral neurologic consequence or associated with neuroblastoma. Posterior fossa tumor can cause symptoms of ataxia, but imaging is negative for tumor in this scenario. Approximately 1% of children with a diagnosis of neuroblastoma present with symptoms including opsoclonus, myoclonus, or ataxia. This can occur in the setting of all stages of neuroblastoma; however, often only small masses are identified. Anatomical image and functional nuclear medicine imaging (I-123 metaiodobenzylguanidine scan) are necessary to fully assess for the presence of neuroblastoma. Because most OMAS associated with neuroblastoma occurs in the setting of nonmetastatic disease, the prognosis for neuroblastoma outcome generally is favorable. However, patients with OMAS are at significant risk for persistent abnormal cerebellar function and progressive neurocognitive decline.

7. You have been asked to see a 10-month-old boy with irritability, periorbital bruising, and proptosis. Cranial CT scan detects a soft tissue mass arising from the zygomatic arch and displacing the orbit. A large, locally invasive retroperitoneal mass also is detected. Tumor biopsy confirms poorly differentiated neuroblastoma with no amplification of *MYCN* and diploid tumor DNA content. Bilateral bone marrow aspirate and biopsies are negative for tumor cells.

Which statement is most accurate?

A. The patient has high-risk neuroblastoma and should receive neoadjuvant chemotherapy followed by surgical resection of the primary tumor and radiation therapy to the primary tumor bed regardless of extent of resection.

B. The patient has high-risk neuroblastoma and should undergo immediate resection of the tumor, followed by chemotherapy and radiation therapy to primary tumor and metastatic disease sites.

C. The patient has intermediate-risk disease and should receive neoadjuvant chemotherapy followed by surgical resection of the primary tumor and radiation therapy to the primary tumor bed regardless of extent of resection.

D. The patient has intermediate-risk disease and should receive neoadjuvant chemotherapy followed by surgical resection of the primary and radiation only to the residual tumor.

E. The patient has intermediate-risk disease and should receive neoadjuvant chemotherapy followed by surgical resection of the primary tumor without radiation therapy.

**Explanation**

The clinical and biologic variables that determine neuroblastoma prognosis and subsequent therapy include tumor stage, patient age, tumor histology, and tumor biologic factors such as presence of MYCN amplification and tumor DNA content. The patient described has metastatic bone disease, defined as International Neuroblastoma Staging System (INSS) stage 4 disease/International Neuroblastoma Risk Group Staging System (INRGSS) stage M. Patients younger than 18 months at diagnosis of INSS stage 4/INRGSS stage M neuroblastoma without tumor MYCN amplification have intermediate-risk neuroblastoma regardless of tumor histology or tumor DNA content. Chemotherapy alone is effective therapy for the majority of children with intermediate-risk neuroblastoma, with an overall survival rate of more than 90%. A prospective clinical trial performed by the Children’s Oncology Group revealed a more than 80% 3-year event-free survival probability and more than 90% 3-year overall survival probability in this group with eight cycles of moderate-intensity chemotherapy. Radiation therapy is reserved for those with disease progression or for life- or organ-threatening symptoms at diagnosis (eg, spinal cord compression with neurologic deficits) that are not immediately responsive to chemotherapy.

8. A 2-week-old infant presents to the hospital with worsening respiratory distress. Exam is notable for tachypnea, edema, hepatomegaly, and blueberry muffin skin lesions. Ultrasound reveals a small suprarenal mass in addition to the hepatomegaly. Blood counts are normal, and bone marrow aspirates and biopsies reveal no tumor cells. A bone scan is negative.

Which of the following statements is correct?

A. This baby has International Neuroblastoma Staging System (INSS) stage 4S/International Neuroblastoma Risk Group Staging System (INRGSS) MS neuroblastoma and will not need therapy because the majority of tumors will spontaneously remit.

B. This baby has hepatoblastoma and should be treated with chemotherapy.

C. This baby has INSS stage 4S/INRGSS MS neuroblastoma and should be treated with chemotherapy.

D. Therapy should not begin until tumor biopsy is obtained.

E. This baby has INSS stage 4/INRGSS M neuroblastoma and should receive chemotherapy.

**Explanation**

The child has the clinical features of INSS stage 4S/INRGSS stage MS neuroblastoma—not stage 4/INRGSS stage M disease—because there is no evidence of metastatic disease in sites other than liver, skin, and specifically not in the bone. Although many INSS stage 4S/INRGSS MS tumors spontaneously regress without adjuvant therapy, patients with worsening organ function, respiratory compromise, or significant hepatomegaly have increased mortality and warrant initiation of cytotoxic therapy. Of infants who succumb to INSS stage 4S/INRGSS stage MS, more than 90% of the deaths occur in children younger than 2 months of age at diagnosis and are attributed to respiratory compromise or disseminated intravascular coagulation or hepatic dysfunction. Initiation of therapy should not be delayed for surgical intervention; however, a biopsy should ultimately be obtained for molecular prognostic features. Tumors that are MYCN amplified are considered high risk and should be treated with intensive multimodal therapy.

9. You are asked to consult on a 2-year-old patient who presents to the emergency department with constipation and refusal to walk. A CT scan demonstrates a paraspinal soft tissue mass extending around the vertebral column and extending into the intraspinal canal, with concern for compression of the spinal cord at L2.

What is the most likely diagnosis?

A. Neuroblastoma

B. Lymphoma

C. Ewing sarcoma

D. Wilms tumor

E. Histiocytosis

**Explanation**

Wilms tumor and histiocytosis occur in young patients but rarely result in intraspinal extension of tumor. Neuroblastoma, Ewing sarcoma, and lymphomas each can present with signs of cord compression. However, neuroblastoma is by far the most likely of these entities to present in a 2-year-old child. Given the presence of neurologic dysfunction, emergent biopsy followed by initiation of therapy is necessary to minimize the risk of long-term neurologic damage. Several retrospective analyses performed in North America and Europe suggest that chemotherapy is sufficient initial therapy that minimizes morbidity associated with laminectomy and neurosurgical resection.

10. Tumor histologic classification is an important prognostic factor for neuroblastoma. Which of the following determines this classification?

A. Age, tumor cell apoptosis, and *MYCN* amplification

B. Age, tumor cell differentiation, and mitosis-karyorrhexis index

C. Age, tumor cell differentiation, and necrosis

D. Age, tumor alveolar histology, and DNA index (ploidy)

**Explanation**

Independent prognostic variables for neuroblastoma include age, stage, histology, MYCN amplification, and DNA index. Histology is graded according to the International Neuroblastoma Pathology Classification, which evaluates for degree of tumor cell differentiation and mitosis-karyorrhexis index as related to age (younger than or older than 18 months) to define favorable or unfavorable histology. Alveolar histology is a histologic subtype of rhabdomyosarcoma.

11. You are asked to see a child who has Hirschsprung disease and, after surgical correction, is noted to have periods of apnea and an elevated serum bicarbonate level. There is a significant family history of childhood malignancy, but the parents cannot recall the types of tumors. This patient probably has which of the following gene mutations and tumor types?

A. Wilms tumor and loss of imprinting of 11p15

B. Neuroblastoma and *PHOX2B* mutation

C. Pheochromocytoma and *TP53* (p53) mutation

D. Neuroblastoma and *ALK* mutation

E. Wilms tumor and 11p13 deletion

**Explanation**

The majority of familial neuroblastomas arise in kindred with mutations in ALK or PHOX2B. Mutations in PHOX2B also contribute to Hirschsprung disease and central congenital hypoventilation syndrome. Neuroblastomas arising with either of these two conditions almost always are associated with missense or triplet repeat expansion mutations in PHOX2B.

12. A patient with high-risk neuroblastoma who presented with a large regionally infiltrative right adrenal mass and femoral bone and bone marrow metastases has recently completed multiagent induction chemotherapy with delayed surgical resection and is in very good partial response. The majority of the primary tumor was resected (more than 95%, leaving 1.5 cm3 residual mass), and all metastatic disease sites are no longer detectable. The patient subsequently received myeloablative chemotherapy with an autologous stem cell transplant, complicated by sepsis and severe veno-occlusive disease and renal dysfunction, but has now recovered, with normal liver and renal function.

Which of the following should subsequent therapy include?

A. No further therapy because the patient is in remission

B. No radiotherapy to the primary tumor bed because of the patient’s history of sinusoidal obstructive disease and risk of radiation-related liver and kidney damage

C. Radiotherapy to the primary tumor bed, with radiation volume based on diagnostic tumor volume

D. Radiotherapy to the primary tumor bed, with radiation volume based on presurgical tumor volume

E. Radiotherapy to the primary tumor bed, with radiation volume based on residual disease at end of induction

**Explanation**

Neuroblastoma is one of the most radiosensitive tumors occurring in childhood. The volume of radiation delivered must at least include the presurgical volume, enabling potentially less toxicity to adjacent organs compared with using diagnostic tumor volume. Doses of 1,260 cGy generally are sufficient to provide excellent local control of high-risk neuroblastoma, provided that the primary tumor has been completely resected. Clinical trials performed by the German cooperative group suggest that residual tumor at the primary site may increase the local failure rate, but this risk may be abrogated by additional radiotherapy to the residual tumor.

13. A patient with high-risk neuroblastoma has completed induction therapy and is in complete response. He subsequently received myeloablative chemotherapy and an autologous hematopoietic stem cell transplant followed by external beam radiotherapy. He has normal organ function and excellent performance score.

What should subsequent clinical management be?

A. No further therapy

B. Isotretinoin for 6 months

C. Continuous low-dose oral cyclophosphamide for 6 months

D. Immunotherapy with dinutuximab, anti-GD2 antibody, combined in alternating cycles with GM-CSF and IL-2 followed by isotretinoin each month for 6 months

**Explanation**

A randomized phase 3 clinical trial demonstrated a 20% 2-year event-free survival advantage for children with high-risk neuroblastoma in first complete or very good partial response receiving the combined immunotherapy (targeting GD2) and isotretinoin regimen compared with isotretinoin alone. A previous German clinical trial demonstrated an improvement in long-term outcome for children who received anti-GD2 immunotherapy compared with a historical cohort who received metronomic cyclophosphamide.

14. A local pediatrician is seeing a 5-year-old survivor of high-risk neuroblastoma who has recently relocated to the area and is being seen for routine well-child evaluation. The pediatrician notices that the child’s speech is mildly delayed, without additional focal neurologic findings. You are called to discuss the potential cause of speech delay and recommend evaluation.

Which of the following is the most appropriate next step in the evaluation of this patient?

A. Refer the patient for neuropsychologic testing due to concern for CNS toxicity of neuroblastoma therapy.

B. Obtain a brain CT image due to concern for CNS metastatic recurrence.

C. Refer the patient for audiologic testing due to concern for chemotherapy-related ototoxicity.

D. Refer the patient for full neurologic assessment due to concern for neuroblastoma opsoclonus myoclonus ataxia syndrome.

**Explanation**

Multimodal therapy is necessary for treatment of high-risk neuroblastoma, including dose-intensive alkylator- and platinum-based chemotherapy. More than 50% of patients who survive high-risk neuroblastoma have hearing deficits associated with platinum therapy, many of whom need amplification. Survivors of high-risk neuroblastoma should have a hearing evaluation at completion of therapy and subsequent evaluations based on noted deficits and potential for continued exposure to ototoxic agents.

15. A 12-year-old girl presents with a large renal mass that is resected and diagnosed as Wilms tumor. Which of the following factors is most predictive of poor outcome?

A. Age greater than 18 months

B. Diffuse anaplasia

C. Presence of pulmonary and liver metastases

D. *WT1* gene mutation

E. *MYCN* amplification

**Explanation**

Although stage, WT1 mutation, 16q, and 1p loss of heterozygosity are prognostic for outcome from Wilms tumor, the most predictive factor for outcome is the presence of diffuse anaplasia. Less than 10% of all Wilms tumors have diffuse anaplasia; however, this group accounts for almost 60% of Wilms tumor–associated deaths. Recent results of the National Wilms Tumor Study 5 have shown that patients with stage 1 tumors with diffuse anaplasia have a 4-year event-free survival rate of 68.4%, which is significantly lower than that of patients with stage 1 tumors with favorable histology. The other answers include factors that are prognostic for neuroblastoma.

16. You are asked to see a 34-week newborn boy with a renal mass, hypertension, and hypercalcemia. Pregnancy was complicated by polyhydramnios. What is the most likely diagnosis?

A. Wilms tumor

B. Rhabdoid tumor of the kidney

C. Congenital mesoblastic nephroma (CMN)

D. Congenital neuroblastoma

E. Congenital acute lymphoblastic leukemia (ALL)

**Explanation**

The differential diagnosis of renal mass in the newborn is CMN, Wilms tumor, rhabdoid tumor, and hamartoma, with more than 90% of CMN occurring in the first year of life. Patients with CMN typically present with a solitary renal mass located in the renal hilum. Polyhydramnios and premature delivery are common, as are elevated blood pressure and serum calcium. Although Wilms can present with elevated blood pressure, prenatal complications are unusual in Wilms or rhabdoid tumor. Congenital ALL can present with an extremely high WBC count and associated renal infiltration (generally not solitary lesions), and serum calcium is more likely to be low in the setting of leukemia-associated tumor lysis syndrome.

17. A 3-year-old boy is referred to you for evaluation of an abdominal mass that was detected while he was playing with his father. The child is well appearing, with blood pressure 120/80 mm Hg, and he has an 8-cm firm mass in the abdomen that crosses the midline. The CBC is normal, and urinalysis reveals 10 to 15 RBCs.

What is the most likely diagnosis?

A. Neuroblastoma

B. Wilms tumor

C. Hepatoblastoma

D. Burkitt lymphoma

E. Mesoblastic nephroma

**Explanation**

Hepatoblastoma, neuroblastoma, and Wilms are all common diagnoses in toddlers. Wilms tumors often present as asymptomatic abdominal masses, with associated hematuria and hypertension as the most common presenting features (occurring in at least 20% of patients).

18. Patients with which of the following features would be most likely to need serial renal ultrasounds to monitor for Wilms tumor?

A. Aniridia and developmental delay

B. Axillary freckles and café au lait spots

C. Protruding tongue, upward slanted eyes, and flattened nose

D. Hirschsprung disease and central hypoventilation

E. Family history of gastrointestinal polyps and adenocarcinoma

**Explanation**

Approximately 30% of patients with WAGR syndrome (Wilms tumor, aniridia, genitourinary malformations, and developmental delay) develop Wilms tumor. Patients with Down syndrome are at risk for leukemia and lymphomas, not solid tumors. Patients with neurofibromatosis (café au lait/freckles) are at risk for CNS tumors and leukemia. Patients with germline mutations in PHOX2B gene are predisposed to Hirschsprung disease and central hypoventilation and neuroblastoma. A family history of GI polyps and GI malignancy requires consideration of familial adenomatous polyposis and associated risk for hepatoblastoma.

19. You have been following a 2-year-old child who was born with an omphalocele, macroglossia, and hemihypertrophy. The child is clinically well but has been followed with serial abdominal ultrasounds. The most recent ultrasound revealed a left-sided renal mass.

Which of the following germline mutations is most likely to be found in this patient?

A. *WT1* gene mutation

B. 16q loss of heterozygosity (LOH)

C. Loss of imprinting at 11p15

D. *ALK* mutation

E. 11q LOH

**Explanation**

The child has classic features of Beckwith-Wiedemann syndrome, which is due to one of several alterations in the germline DNA of the WT2 gene at 11p15. The net result is a loss of imprinting that provides a growth advantage and tumor susceptibility. The tumor will obviously contain the same genetic defect that is present in the germline (constitutional) DNA. WT1 gene mutations are associated with WAGR (Wilms tumor, aniridia, genitourinary malformations, and developmental delay) and Denys Drash syndrome and present in sporadic tumors, whereas 16q LOH is also present in sporadic tumors. ALK mutations are associated with familial neuroblastoma, and both ALK and 11q LOH are seen in sporadic neuroblastoma.

20. You are caring for a child with newly diagnosed Wilms tumor. The patient is otherwise well appearing, with no congenital anomalies and no family history of cancer. Which of the following genetic alterations might be found in the tumor cells?

A. Amplification of *WT1*

B. Translocation of chromosomes 2 and 5

C. Amplification of *MYCN*

D. Loss of heterozygosity (LOH) at 1p or 16q

E. Translocation involving *PAX3* or *PAX7*

**Explanation**

Several genetic aberrations have been described in Wilms tumor, including loss of heterozygosity (LOH) at 1p or 16q, WT1 mutation, beta-catenin, and loss of imprinting of IGF-2; each of these occur in at least 10% of Wilms tumor samples. Mutations in WT1 and WT2 genes occur in Wilms tumor but not amplification. Amplification of MYCN occurs in neuroblastoma and some brain tumors. Translocations of chromosomes 2 and 5 are seen in anaplastic large cell lymphoma; translocations involving PAX3 and PAX7 are seen in the alveolar subtype of rhabdomyosarcoma.

21. A 2-year-old boy presents with an asymptomatic abdominal tumor that crosses the midline on exam. Radiographic studies confirm a left renal mass with extension into the inferior vena cava; no pulmonary or liver metastases are noted. The mass and thrombus are resected, and pathology reveals an intact tumor mass that extends beyond the pseudocapsule and invades into the renal sinus, but no tumor is at the surgical margin.

What is the stage of this tumor?

A. Stage 1

B. Stage 2

C. Stage 3

D. Stage 4

E. Unable to determine without degree of anaplasia

**Explanation**

The National Wilms Tumor Staging System, used throughout North America, is dependent on degree of resection, presence of tumor at margin, presence of tumor spillage or malignant ascites, and presence of hematogenous spread. This patient has stage 2 disease because there is no tumor at the surgical margins despite involvement of renal sinus or the presence of renal thrombus. Stage 3 is defined as biopsy only, disease at the margin, spillage, or malignant ascites.

22. A 6-year-old girl presents with a history of hematuria and right upper leg pain. A CT scan of the abdomen and pelvis reveals a solitary renal mass. Plain film of the right femur suggests abnormality of the femur. The patient undergoes nephrectomy. Pathology reveals a malignancy, with cords of pale-stained tumor cells and abundant extracellular matrix.

What evaluations should be performed to assess metastatic spread?

A. Pathologic review of abdominal lymph nodes and CT scan of the chest

B. Bone scan and CT scan of the brain

C. I-123 metaiodobenzylguanidine whole-body scintigraphy and bone marrow biopsy

D. Bone scan and bone marrow biopsy

E. CT scan of the chest and bone marrow biopsy

**Explanation**

Differential diagnosis of primary renal tumor in a pediatric patient includes Wilms tumor, clear cell sarcoma, and Ewing sarcoma, whereas lymphoma and neuroblastoma can present with direct renal invasion, and leukemia and lymphoma can present with metastatic involvement. The information provided suggests a primary renal mass. Wilms is the most common primary renal tumor; however, leg pain raises the possibility of bone involvement, an unusual site of metastatic spread for Wilms tumor. Furthermore, the pathologic characteristics of Wilms, lymphoma, and Ewing are characterized by small, round blue cells, and in the case of Wilms, stromal and glomerular elements are not present. Conversely, clear cell sarcoma best fits the pathologic description provided. Clear cell sarcoma often is associated with bone metastatic disease; additional sites of metastases include brain and soft tissue. Clear cell sarcoma has a significantly higher risk of recurrence and death from disease than Wilms tumor.

23. A 19-year-old man presents to his physician with headache, tachycardia, diaphoresis, and hypertension. A 24-hour urinary fractionated metanephrine and catecholamine test reveals elevated normetanephrine. An abdominal ultrasound reveals a large right adrenal mass and an additional mass at the bifurcation of the aorta.

Which is the correct next medical intervention?

A. The patient should undergo surgical biopsy to confirm a diagnosis.

B. Antianxiolytic therapy should be initiated.

C. The patient should receive medical therapy to control hypertension and promote volume expansion.

D. The patient should undergo genetic testing for familial cancer disorders.

**Explanation**

The classic triad of symptoms for patients with pheochromocytoma is headache, diaphoresis, and tachycardia. Either sustained or paroxysmal hypertension is present in the majority of patients. The diagnosis is made based on hypersecretion of catecholamine metabolites and followed by radiologic confirmation of a tumor. Resection of the tumor is the mainstay of treatment. However, it is associated with high morbidity due to hypertensive crises, arrhythmia, and organ failure. Preoperative pharmacologic therapy is necessary for all patients with probable pheochromocytoma, consisting of combined α- and β-adrenergic blockade and high-salt diet to control hypertension and provide volume expansion. Though not required urgently, genetic testing should be considered in all pediatric patients as well as those with multifocal disease or nonadrenal primary disease because there is an association with several familial cancer syndromes, including von Hippel-Lindau syndrome, multiple endocrine neoplasia type 2, and neurofibromatosis.

24. A 10-year-old black boy with known sickle cell disease presents to the emergency department with flank pain. He is hospitalized for management of presumed acute vaso-occlusive disease. During his hospital stay, hematuria is documented. Urinalysis is not consistent with infectious etiology, and the patient is afebrile. An abdominal ultrasound reveals a mass in the right kidney.

What is the most likely diagnosis?

A. Renal lymphoma

B. Rhabdoid tumor

C. Renal abscess

D. Renal medullary carcinoma

**Explanation**

Renal medullary carcinoma is a rare renal tumor that effects older pediatric and young adult patients with sickle cell trait or sickle cell disease. In pediatric patients, boys are three times more likely to develop it than girls. The tumor arises from the terminal collecting ducts or papillary epithelium associated with chronic hypoxia caused by sickle cell disease. Other tumors arising in the renal medulla include lymphoma and rhabdoid tumor, although both are unlikely in this scenario. Lymphomatous involvement of the kidney generally occurs in the setting of widespread disease and not isolated mass. Rhabdoid tumor of the kidney generally occurs in children younger than 2 years of age. Similarly, Wilms tumor can occur in adolescents but is more common in young children.

25. A 9-month-old previously healthy infant presents with abdominal distension. Physical exam is otherwise unremarkable. Radiographic imaging reveals bilateral adrenal masses. Family history is notable for diagnosis of neuroblastoma in the maternal aunt and maternal grandfather.

Which germline genetic abnormality is most likely to be present?

A. *NF1* mutation

B. *PHOX2B*

C. *ALK*

D. *TP53*

**Explanation**

Neuroblastoma usually arises sporadically in infancy and young childhood. About 1% to 2% of children with neuroblastoma have familial neuroblastoma with autosomal dominant inheritance, with the most common germline mutations in *ALK* or *PHOX2B*. *ALK* is a tyrosine kinase receptor that has a role in cell proliferation. *PHOX2B* germline mutations are typically associated with additional neurologic abnormalities, including Hirschsprung disease and central hypoventilation, and therefore are unlikely in this scenario.

26. A 7-year-old girl with a right kidney mass and numerous bilateral pulmonary metastases undergoes an upfront nephrectomy. Pathology reveals a favorable histology Wilms tumor, with an intact tumor mass confined to the kidney. The patient undergoes 6 weeks of chemotherapy with vincristine, actinomycin-D, and doxorubicin with flank radiotherapy (10.5 Gy).

What factors might influence decisions for subsequent therapy?

A. Complete radiographic resolution of pulmonary metastases

B. Previous occurrence of hematologic toxicity

C. Age of the patient

D. Presence of *WT1* mutations

**Explanation**

Whole lung radiation has been a mainstay in the management of Wilms tumor with pulmonary metastases. Excellent outcomes have been observed with this approach, but with significant late effects including pulmonary fibrosis, cardiac dysfunction, and secondary malignancies. Based on observations of excellent outcomes of patients who had rapid clearance of pulmonary metastases with chemotherapy, the Children’s Oncology Group conducted a phase 3 study (ARENT0533) eliminating whole lung irradiation for patients who had complete radiographic resolution of pulmonary metastases after 6 weeks of chemotherapy. For patients with complete resolution, 4-year event-free survival and overall survival estimates were 79.5% (95% CI, 71.2%-87.8%) and 96.1% (95% CI, 92.1%-100%), respectively. Expected versus observed event rates were 15% and 20.2% (*P* = .052), respectively. Despite a slightly higher than expected rate of events, patients maintained excellent outcomes with the elimination of whole lung radiotherapy.

Overall toxicity of standard chemotherapy includes acute hematologic toxicity and potential for organ dysfunction, including liver and cardiac toxicity. However, it is unlikely that therapy would need to be significantly revised for hematologic toxicity. Although diagnosis of Wilms at an older age is associated with worse outcome, therapy is not adjusted. Although somatic mutations in *WT1* are seen in approximately 20% of patients with Wilms tumor, therapy is not adjusted.

27. A 9-month-old girl is seen by her pediatrician for fussiness and decreased oral intake. Physical exam reveals a large, nontender abdominal mass. Imaging reveals an 8 × 5 cm right adrenal mass encasing the descending aorta and inferior vena cava. Urinary catecholamine levels are more than two standard deviations above normal. Distant metastases are not present on I-123 metaiodobenzylguanidine scintigraphy or bilateral bone marrow examinations.

How would you counsel this patient’s family on recommended therapeutic intervention?

A. Complete resection of the tumor with negative surgical margins should be attempted.

B. The patient has neuroblastoma and should be treated emergently with chemotherapy.

C. The tumor should be biopsied.

D. The tumor is likely to spontaneously regress and can be closely observed with serial imaging.

**Explanation**

This young child probably has a localized neuroblastoma, based on age, site of disease, and catecholamine secretion. However, formal diagnosis of neuroblastoma requires tumor biopsy for histopathologic confirmation or bone marrow presence of tumor clumps and elevated catecholamine. Tumor histopathologic findings according to the International Neuroblastoma Pathologic Criteria and biologic characteristics including presence of *MYCN* amplification, segmental chromosomal aberrations, and tumor ploidy are necessary to assign appropriate treatment. Although surgical resection of localized neuroblastoma can be curative, the presence of image-defined risk factors such as encasement of large vascular structures is associated with increased surgical morbidity and mortality and decreased event-free survival. Therefore, the tumor should be biopsied to confirm diagnosis and obtain necessary biologic characteristics. Although reports from Germany suggest the potential for spontaneous regression of locoregional neuroblastoma occurring in infants, it is limited to patients with biologically favorable neuroblastoma confirmed by biopsy.