

Emergency Department Presentation of Childhood Cancer

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KEYWORDS

• Cancer • Pediatric • Tumor • Leukemia • Diagnosis

Cancer is an uncommon diagnosis in children and occurs at a much lower frequency than in adults. The annual incidence rate for cancer in children (aged 0–19 years) is 165 cases per million, with approximately 12,000 children diagnosed with malignancies in the United States each year.¹ Due to the rarity and the often nonspecific signs and symptoms of malignancy, early detection of cancer in children can be difficult. Early diagnosis is critical in some cases and can result in a better prognosis. With current treatment, more than two thirds of children who develop cancer will be cured of their disease. However, for many children with cancer, disseminated or advanced disease at diagnosis requires more intensive therapy and leads to poorer outcomes.

Children who are diagnosed with cancer may present to primary care providers or to the Emergency Department (ED) with a variety of complaints. Many children with cancer appear remarkably well at the time of initial diagnosis. Conversely, a child with a curable cancer may be severely ill at presentation, making appropriate initial management critical. The manifestations of certain types of cancer constitute medical emergencies that require acute intervention. Therefore, knowledge of the most common presentations of childhood cancer and appropriate initial management is essential.

CHILDHOOD MALIGNANCIES

Cancer is the second leading cause of death in children in the United States and is the most common cause of death due to disease.² The types and patterns of malignancies seen in children are different from those seen in adults and vary with the age of the child.

Acute leukemias are the most common type of cancer, accounting for 26% of all cancer diagnoses in children.¹ Brain tumors and lymphomas are the next most common categories of neoplasm in children. All of these diagnoses, along with

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embryonal solid tumors outside the central nervous system (CNS) (neuroblastoma, renal tumors, malignant bone tumors, and soft-tissue sarcomas) account for more than 80% of childhood malignancies. The incidence of certain types of cancer varies significantly with age. For example, neuroblastoma and Wilms tumor are uncommon over the age of 5 years. In contrast, Hodgkin lymphoma, which is rare in young children, is the most common cancer diagnosed in adolescents aged 15 to 19 years.¹ Carcinomas are exceedingly rare in children and young adults.

GENERAL SIGNS AND SYMPTOMS OF CHILDHOOD CANCER

The initial symptoms in children who are diagnosed with cancer often mimic those of other, more common childhood illnesses (**Box 1**). Fever is commonly seen at the time of presentation in many childhood cancers, particularly with leukemia and lymphoma. However, fever is a nonspecific sign, and most children with fever of unknown origin will not be found to have a malignancy.³ Malaise, fatigue, vomiting, and weight loss are other nonspecific, nonlocalizing symptoms that may be associated with cancer in children. Although these symptoms may be manifestations of a variety of diseases such as infectious or autoimmune disorders, malignancy should always be considered in the differential diagnosis. Other cancer-associated symptoms typically relate to the site of involvement.

CENTRAL NERVOUS SYSTEM TUMORS

Brain tumors are the most common solid tumor in children, and are the second most common childhood cancer.⁴ More than 2000 children in the United States are diagnosed with a malignant CNS tumor every year.⁴ If histologically benign tumors are included, the overall incidence of brain tumors is significantly higher.⁵ Gliomas, which can occur anywhere in the neuro-axis, are the most common histologic group of brain tumors and may be benign or malignant. Medulloblastoma, a neuronal tumor of the posterior fossa, is the most common malignant brain tumor in children.⁶ CNS tumors are more common in patients with certain underlying conditions, such as neurofibromatosis or tuberous sclerosis.

The history and physical examination are critical in the recognition of an undiagnosed CNS tumor and should guide the ED physician in determining whether neuroimaging is warranted. The presentation of CNS tumors can be simplified into two categories: increased intracranial pressure (ICP) and localizing signs/symptoms. Both should be carefully considered if a CNS tumor is suspected, and the severity of presentation will determine the urgency of further evaluation and management.

Box 1

Nonspecific signs and symptoms of childhood cancer

- Fever
- Malaise
- Fatigue
- Vomiting
- Weight loss
- Behavior change
- Decline in school performance

Signs and symptoms of increased ICP may be vague and generalized, or can be severe and life-threatening. Increased ICP typically occurs as a result of obstruction of normal cerebrospinal fluid flow, and the classic presentation is headache, vomiting, and mental status decline. However, headache and vomiting are common complaints in the pediatric population. Children with newly diagnosed brain tumors have often been initially treated for flulike illness or viral gastroenteritis, and have had multiple visits to primary care providers or EDs before the brain tumor is recognized. For medulloblastoma and other malignant tumors, the time to diagnosis from the onset of the symptoms is typically 2 to 4 weeks, but benign tumors can cause vague or chronic symptoms for months or even years. In addition, the prevalence of headache in elementary school children is approximately 40% to 50% and up to 60% to 80% in the high school years.⁷ The ED physician must perform a complete neurologic examination to recognize which children with these common complaints require further evaluation for brain tumor.

A large study of 3300 newly diagnosed pediatric brain tumor patients performed by the Childhood Brain Tumor Consortium reported that nearly two thirds of patients had chronic or frequent headaches before their first hospitalization.⁸ Typically, the headaches associated with brain tumors gradually worsen. A clear indicator of increased ICP is a headache that awakens a child from sleep, especially if it leads to vomiting or is associated with an objective neurologic finding.

Location of the headache is rarely helpful, but occipital headaches should always be further evaluated with neuroimaging. The structures of the posterior fossa are innervated by branches of upper cervical roots, which also innervate the back of head. An ED study of 150 children with acute onset of headache identified only two children with occipital headaches, both of whom had posterior fossa tumors.⁷ Constant occipital headache and neck pain with hyperextension is an ominous sign of tonsillar herniation into the foramen magnum and requires immediate neurosurgical attention.

So which patients with headaches in nonoccipital locations need neuroimaging? The Childhood Brain Tumor Consortium Study showed that more than 98% of patients with newly diagnosed brain tumors presenting with headache also had objective neurologic findings.⁸ A similar but smaller study also revealed that most patients diagnosed with brain tumors who presented without focal neurologic findings had a history of seizure.⁹ Objective neurologic findings in the larger study included mental status changes, abnormal eye movements, optic disc distortion, asymmetric motor or sensory examination, coordination problems, or abnormal deep tendon reflexes. Therefore, a thorough and complete neurologic examination must be performed when evaluating a child with headache. Recognition of some of these findings is straightforward, but papilledema can be difficult to identify if the physician is not comfortable with fundoscopic examination. This bedside skill should be practiced routinely with all patients so that physicians become comfortable with this critically important assessment tool. **Box 2** summarizes recommendations on the role of neuroimaging for children with headaches.

Signs of increased ICP that are unique to infants and young children include macrocephaly and the “setting sun sign” of the eyes. The head circumference should be measured in every young child being evaluated in the ED, especially if the presenting symptoms are difficult to interpret. It is important to recognize that cranial sutures can separate even after the fontanel has closed in toddlers with increased ICP. The “setting sun sign” refers to downward deviation of the eyes as a result of pressure on the cranial nerves that control eye movements. The eyes are forced downward, often with sclera visible above the iris, and pupillary responses are typically sluggish.

Box 2**Indications for magnetic resonance imaging in children with headache**

- Occipital location
- Association with seizures
- Association with recumbent position
- Association with vomiting
- Exacerbation with straining
- Presence of ominous signs
 - Cushing's Triad (bradycardia, hypertension, irregular respirations)
 - Altered mental status
- Presence of objective neurologic findings
 - Abnormal eye movements
 - Optic disc distortion or papilledema
 - Asymmetric examination (motor, sensory, deep tendon reflexes)
 - Coordination problems (ataxia, dysmetria)
- Macrocephaly in infants and toddlers

The setting sun sign is a late and ominous sign of elevated ICP in young children, and is often associated with irritability, lethargy, and poor feeding. These nonspecific signs should trigger consideration of an undiagnosed brain tumor.

Localizing signs of CNS tumors may include seizures, cranial nerve dysfunction, endocrine dysfunction, cerebellar dysfunction (ataxia or dysmetria), bowel or bladder dysfunction, abnormal or asymmetric strength, abnormal sensation, or asymmetric deep tendon reflexes.¹⁰ Although less easily classified as localizing signs, declining school performance and behavior changes are common complaints in children and adolescents diagnosed with a brain tumor.

As with headaches, seizures due to other causes occur more commonly than brain tumors and do not always warrant emergent neuroimaging. However, unless the presentation is clearly consistent with simple febrile seizure or absence seizure, magnetic resonance imaging (MRI) of the brain is recommended because the consequences of failing to recognize the presence of a brain tumor may be severe. Certainly, any EEG showing signs of a focal abnormality warrants further evaluation with MRI. The American Academy of Neurology has outlined a detailed practice parameter for evaluation of the first nonfebrile seizure, including specific indications for neuroimaging.¹¹

Spinal cord compression is a critically important localizing sign to recognize and treat emergently because appropriate management can reverse deficits and prevent further devastating complications. Compression can be due to intrinsic CNS tumor, bony disease originating in a vertebral body, or paraspinous soft-tissue tumor infiltrating through an intervertebral foramina. Compression can occur with sarcomas, lymphoma, leukemia, neuroblastoma, germ cell tumors, spinal cord tumors, and metastatic brain tumors. Back pain occurs in 80% of children with cord compression, and any child known or suspected to have cancer who also has back pain should be carefully evaluated for cord compression.¹² Spinal cord compression can also present with progressive weakness or sensory abnormalities, and paraplegia or quadriplegia

can occur rapidly. Fecal or urinary incontinence may be a sign of compression at the level of the cauda equina, and should not be disregarded, especially in a child with previous control of the bowel and bladder. A careful neurologic examination is essential, with attention to strength, reflexes, sensory abnormalities, musculoskeletal and sphincter tone, and localized tenderness to percussion of the vertebral column. Any child with an identified neurologic deficit and any child who refuses to walk or is unable to walk should undergo urgent imaging of the entire spine by MRI. Those with localizing back pain and a normal examination should also undergo imaging within 24 hours, and a complete neurologic examination should be repeated routinely by a physician at least every 4 hours.

There are a few other specific localizing signs that should be highlighted. Any child with an acquired eye movement disorder and any infant with eye movement abnormalities beyond 2 to 3 months of age should be referred to ophthalmology and undergo MRI of the brain. Although there are postviral and congenital causes of fourth and sixth nerve palsies, the presence of a brain tumor must be excluded. These cranial nerve abnormalities are best identified by complaint or recognition of diplopia (vertical or horizontal) or head tilt on examination. Another easily recognized eye finding is Parinaud ophthalmoplegia, which is a feature of pineal region tumors. Patients with this finding have impaired upward gaze, a sluggish pupillary response to light, and a phenomenon called convergence retraction nystagmus. The first two elements of this triad can be recognized with simple neurologic examination. It may be more difficult to recognize convergence retraction nystagmus without the assistance of an ophthalmologist, but it can sometimes be elicited by having the patient attempt to look up. This will result in irregular, jerky flickering of the eyes, and a more subtle finding of inward rotation and retraction of the eyes in the orbit. Finally, precocious pubertal development may also be a sign of a tumor affecting the hypothalamic-pituitary axis or a germ cell tumor that is secreting human chorionic gonadotropin (hCG).

If a decision is made to pursue neuroimaging, MRI of the brain or spine with and without contrast is the ideal study to perform. However, if the patient is hemodynamically or neurologically unstable due to increased ICP, urgent CT scan of the head without contrast may be appropriate. **Fig. 1** shows an example of a common presentation of childhood brain tumors: a posterior fossa mass causing obstructive hydrocephalus. In any case of suspected brain tumor, neurosurgery should also be consulted immediately for further evaluation and management. MRI of the entire spine should not be delayed by obtaining spine radiographs in the child with suspected cord compression as less than 50% of patients with cord compression will have abnormal findings on plain films.¹³

Interventions to consider while awaiting neurosurgical management of a patient with increased ICP include initiation of dexamethasone, mannitol, hypertonic 3% saline, or intubation for airway protection and controlled hyperventilation. All of these measures can minimize edema and decrease intracranial pressure. Intravenous (IV) dexamethasone should be given as a bolus of 1 to 2 mg/kg (10 mg maximum dose) in the ED. Dexamethasone can be maintained on admission at approximately 1.5 mg/kg/day divided every 6 hours (maximum 4 mg/dose).¹⁴ Mannitol 20% at 0.5 to 1 g/kg by slow IV infusion or 3% saline infusion can also be considered in consultation with neurosurgery. Hyperventilation to a systemic pCO₂ of 30 to 35 mmHg can reduce cerebral blood flow and therefore temporarily decrease ICP as well. Hyperventilation to pCO₂ levels less than 30 mmHg is no longer recommended. Narcotic administration for pain control should be avoided or used with extreme caution in patients who are not already intubated because the potential sedation can lead to increased pCO₂, exacerbation of increased

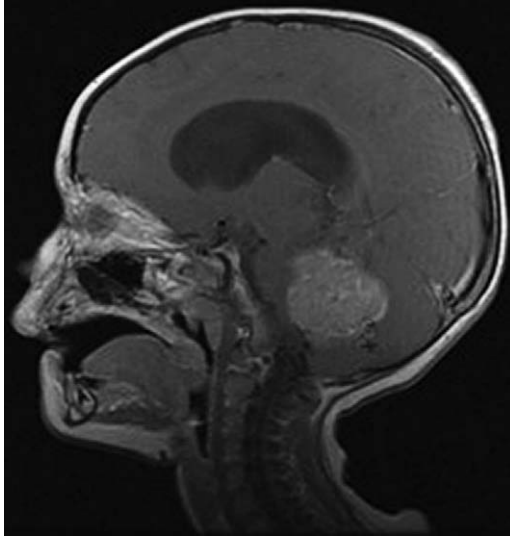


Fig. 1. Hydrocephalus due to newly diagnosed posterior fossa tumor.

ICP, and rapid decline in clinical status. In coordination with the neurosurgery service, a decision should be made as to whether the patient will be admitted to a critical care unit, admitted to a neurosurgical unit, or taken directly to the operating room.

Dexamethasone should also be initiated immediately for patients with suspected cord compression (see dose recommendations discussed earlier). Although neurologic function may improve with steroids, decompression of the cord is still necessary. Neurosurgery, radiation oncology, and pediatric oncology should be consulted urgently to determine the appropriate mode of decompression. Although urgent chemotherapy or radiation therapy can be helpful in treatment-sensitive tumor types, surgical decompression is usually the most reliable approach.

In less urgent scenarios whereby a CNS tumor is being considered, MRI can be performed after admission to the hospital or in the outpatient setting with close follow-up and direct communication with the primary care provider and consultant, such as ophthalmology or neurosurgery. However, any patient with signs or symptoms of increased ICP, cord compression, or new localizing neurologic deficit should have immediate imaging performed in the ED.

HEMATOLOGIC MALIGNANCIES

Acute Leukemia

Acute leukemia is the most common cancer in children. Approximately 3500 children are diagnosed with acute leukemia every year in the United States,¹⁵ and acute lymphoblastic leukemia (ALL) accounts for approximately 75% of these cases.¹⁶ ALL can occur at any age, but the peak incidence is between the ages of 2 and 5 years.¹⁷ For acute myelogenous leukemia (AML), the second most common type of leukemia in children, the incidence rate remains stable throughout childhood.

Presenting features of acute leukemia are due to marrow infiltration with leukemia “blasts” and resultant anemia, thrombocytopenia, and neutropenia. The most common symptoms and physical findings at diagnosis are listed in **Table 1** and

Table 1
Presenting features of childhood leukemia and lymphoma

Acute Leukemia	Lymphoma
<ul style="list-style-type: none"> • Fever • Pallor • Bleeding: petechiae, purpura • Bone pain/limp • Lymphadenopathy • Splenomegaly/hepatosplenomegaly • Gingival hyperplasia • Leukemia cutis or chloroma 	<ul style="list-style-type: none"> • Painless lymphadenopathy • Mediastinal mass • Pleural effusion • Abdominal mass • Fever • Drenching night sweats • Pruritis • Unintended weight loss

include any or all of the following: fever, pallor, bleeding (often manifested as petechiae or purpura), bone pain (often manifested as a limp), lymphadenopathy, splenomegaly, or hepatosplenomegaly.¹⁸ The peripheral white blood cell count may be high, low, or even normal at presentation. Viral infections, such as those due to Epstein-Barr virus (EBV) and parvovirus can result in hematologic abnormalities similar to those seen in patients with acute leukemia. Lymphadenopathy, splenomegaly, and “atypical” lymphocytosis often seen with EBV infections can sometimes be difficult to distinguish from acute leukemia.¹⁹ T cell ALL, which accounts for approximately 15% of ALL cases in children, often presents with a high white blood cell count and a mediastinal mass.¹⁸

Children with AML often present in a similar manner to those diagnosed with ALL. However, manifestations of extramedullary involvement are more common in AML and include gingival hyperplasia, leukemia cutis, and tumors composed of AML blasts called chloromas. Gingival hyperplasia in a child is unusual and should raise alarm to the presence of a myelogenous leukemia, even if no other signs or symptoms are present. Leukemia cutis can be recognized as nontender plaques or nodules that are blue-purple in color or sometimes colorless. Chloromas can occur anywhere, but are common in the orbit or peri-orbital region.

If a diagnosis of leukemia is being considered on presentation to the ED, diagnostic evaluation should start with a complete blood count (CBC) with manual differential and peripheral smear. Acute leukemia often presents with leukocytosis or cytopenias. Leukemia “blasts” are often present (**Fig. 2**), although lack of peripheral blasts does not rule out leukemia. Most children diagnosed with acute leukemia will have more than 1 cytopenia on the initial CBC. However, many other illnesses result in cytopenias and can have findings on CBC that mimic acute leukemia. These include viral or bacterial infections, autoimmune processes such as idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia, solid tumors with metastases to bone marrow, and bone marrow failure syndromes such as aplastic anemia.

A new diagnosis of leukemia is often suspected before the patient arrives at the ED because the primary care provider has already found reason to perform a CBC, and the laboratory has informed the provider that cytopenias or leukemia “blasts” are present. In this case, the pediatric hematology/oncology team should be involved early and the ED evaluation should be focused on detecting life-threatening complications and important supportive care interventions. **Box 3** summarizes the initial evaluation and care of a newly diagnosed acute leukemia patient. If all elements are performed or started in the ED, the safety of the patient will be maximized and initiation of chemotherapy can be expedited. This checklist takes into account the most severe and common complications at the time of diagnosis, as well as some of the diagnostic

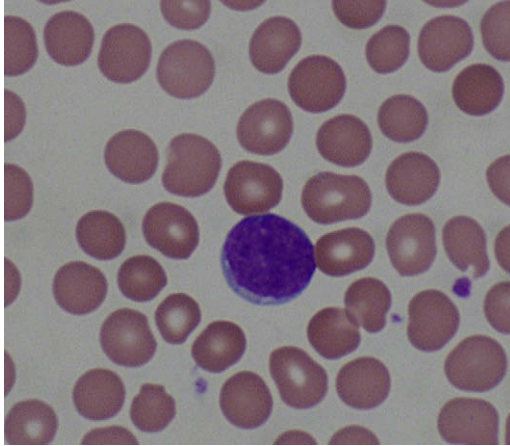


Fig. 2. Lymphoblast on a peripheral blood smear, often seen at the time of diagnosis of acute lymphoblastic leukemia (Wright-Giemsa, original magnification 600 \times). Note the large size of the cell relative to red blood cells, and high nuclear to cytoplasmic ratio. (Courtesy of Nicky Leeborg, Portland, OR)

and baseline laboratory tests needed to allow the oncology team to plan specific treatment.

The common emergent complications that the ED physician needs to consider when assessing a child with suspected leukemia include tumor lysis syndrome, severe coagulopathy, hyperleukocytosis, and a mediastinal mass causing compression of the superior vena cava or trachea. Tumor lysis syndrome (TLS) is the result of release of intracellular contents of leukemia blast cells as they lyse spontaneously or in response to therapy. Serious cell lysis usually does not occur at presentation unless the white blood cell (WBC) count is high. Levels of potassium, phosphorus, and uric acid may increase beyond the excretory capacity of the kidneys. TLS is reviewed in detail in an accompanying article in this issue.

The release of granules particular to some AML blasts can lead to severe coagulopathy and disseminated intravascular coagulopathy (DIC). Hyperleukocytosis (defined as WBC $>100,000/\text{mm}^3$) can lead to increased viscosity of blood and aggregation in microvasculature,¹⁴ particularly in AML. The most severe complications of hyperleukocytosis are respiratory failure, hemorrhage (CNS, gastrointestinal, pulmonary, pericardial), and CNS complications due to poor oxygenation. Patients with hyperleukocytosis who are critically ill may present with hypoxia, dyspnea, headache, somnolence, confusion, or blurred vision. Hyperviscosity syndromes are also reviewed in more detail in another article in this issue. The management of a patient with a mediastinal mass is discussed in the lymphoma section of this article.

Once a diagnosis of leukemia is suspected, peripheral IV access should be established and laboratory tests should be obtained, including CBC with manual differential, peripheral blood smear, coagulation profile (PT/PTT/fibrinogen), type and screen, and certain chemistries (uric acid, creatinine, potassium, phosphorus, and calcium). If the patient is febrile ($\geq 38.3^\circ\text{C}$) by history or at presentation, a blood culture should be obtained and a broad-spectrum IV antibiotic, such as ceftazidime, should be started to offer broad-spectrum empirical coverage. These patients typically have functional neutropenia, even if their neutrophil count is normal, and they are at high risk for gram-positive and gram-negative bacteremia or sepsis.

Box 3**Checklist for known or suspected new diagnosis of acute leukemia**

- History and careful physical examination
- Measure accurate weight and height
- Place peripheral IV line(s) for supportive care (unless mediastinal mass suspected, then consider chest radiography first)
- Laboratory evaluation
 - CBC with manual differential
 - Peripheral smear
 - Critical chemistries: uric acid, creatinine, potassium, phosphorus, calcium
 - Coagulation profile: prothrombin time [PT], partial thromboplastin time [PTT], fibrinogen
 - Type and screen
 - If febrile, blood culture (aerobic, anaerobic, and fungal)
- Obtain chest radiograph
- Start hydration at 125 mL/m²/h unless fluid load contraindicated
 - Order alkalinized fluids (D₅ 1/4 NS with 30 mEq/L sodium bicarbonate)
 - Start available fluid (eg, D₅ 1/2 NS) and run until alkalinized fluid available
 - Do not give potassium
- Start allopurinol
- If febrile, start empirical broad-spectrum antibiotic (ie, ceftazidime 50 mg/kg IV)
- Order and initiate blood products as indicated
 - If bleeding, give platelets, fresh frozen plasma (FFP), or cryoprecipitate
 - If severely anemic, start slow transfusion of packed red blood cells

Once IV access is established, IV fluids should be started immediately to minimize the potential complications of TLS. Alkalinized fluids are preferred, unless the serum phosphorus level is elevated, because this allows increased solubility and excretion of uric acid and its breakdown products in alkalinized urine. If fluids with sodium bicarbonate are not immediately accessible, fluids available in the ED should be run until the alkalinized fluids arrive. D₅ 1/4 NS with 30 mEq/L sodium bicarbonate to run at 125 mL/m²/h (approximately twice maintenance) should be ordered. Until this arrives, D₅ 1/2 NS should be run at the same rate. D₅ 1/2 NS without bicarbonate should be used if phosphorus is elevated or if recombinant urate oxidase (Rasburicase) is being given for hyperuricemia. Potassium should never be given, even if there is moderate hypokalemia, as serum potassium levels may increase quickly to dangerous levels in the setting of tumor lysis. Serum potassium should be closely followed and the urine output maintained at 3 mL/kg/h or greater to minimize the complications of TLS.¹⁴ Mannitol or lasix can be used to help maintain urine output if the patient is hemodynamically stable and there is normal kidney function. Allopurinol should be started routinely in all newly diagnosed leukemia patients, because tumor lysis and therefore hyperuricemia will increase when therapy is started. The first dose can be ordered in the ED (100 mg/m² [approximately 3 mg/kg] by mouth).

If the laboratory results show elevation in potassium, creatinine, or uric acid, urgent consultations should be made with oncology, nephrology, and critical care. Immediate dialysis may be deemed necessary by nephrology in some cases, and should not be delayed. If dialysis is not indicated, the electrolyte disturbances can be managed with close monitoring of laboratory tests and urine output. If the uric acid level is severely elevated (>8 mg/dL) or is rising quickly, or if the creatinine level is elevated, allopurinol should be replaced by recombinant urate oxidase (Rasburicase) (0.15–2 mg/kg/d intravenously in a single dose, maximum dose 7.5 mg). Rasburicase causes rapid reduction in the uric acid level by catalyzing the oxidation of uric acid to allantoin, which is a highly soluble metabolite that is readily excreted by the kidneys. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. If phosphate is elevated (≥ 6.5 mg/dL), and the calcium \times phosphorus product (calcium in mg/dL \times phosphorus in mg/dL) is more than 60, calcium phosphate may crystallize in the renal tubules and microvasculature,¹⁴ potentially leading to renal failure. In addition to routine measures of hydration or even diuresis, aluminum hydroxide, sevelamer (Renagel), or calcium carbonate can be given to bind phosphate. Hyperkalemia can lead to ventricular arrhythmia and death, and should be managed urgently in the ED. Calcium gluconate may be used for life-threatening cardiac effects. Use sodium bicarbonate (1–2 mEq/kg IV), nebulized albuterol, and glucose/insulin (0.5 g glucose/kg/h with 0.1 unit insulin/kg/h) to drive potassium into cells.¹⁴ The use of sodium polystyrene sulfonate (Kayexalate) to bind potassium can be used in nonurgent situations, and is unlikely to be indicated in the ED setting.

There will likely be institutional differences in the management of hyperleukocytosis, but any patient with WBC greater than 100,000/mm³ needs to be considered carefully for leukapheresis or exchange transfusion, especially if there is suspicion that the patient may have myelogenous leukemia. A pediatric oncologist and a pediatric critical care physician should be consulted immediately for any patient who presents with a WBC greater than 100,000/mm³.

Typically, transfusions of blood products can be started once the patient is admitted. If there is active bleeding due to DIC, transfusions of platelets, FFP, or cryoprecipitate should be ordered urgently in the ED. Severe coagulopathy due to the release of contents of granules in the blasts is common with AML. As with the electrolyte disturbances of tumor lysis, coagulopathy can worsen with the initiation of therapy. Severe anemia can lead to heart failure and should be considered when transfusion of packed red blood cells (pRBCs) is being ordered. Typically, 5 mL/kg/h for a total of 15 mL/kg can be given, but if the hemoglobin level is less than 5 g/dL, the transfusion should be given more slowly. As pRBCs will increase blood viscosity, pRBC transfusions should be avoided in patients who present with hyperleukocytosis. However, patients with platelet count less than 30,000/mm³ and hyperleukocytosis should receive platelets urgently because the risk of hemorrhagic stroke is significant and platelets contribute little to blood viscosity. All blood products should be leukocyte-reduced and irradiated.

The disposition for admission will depend on the clinical status of the patient, the laboratory results, and the results of imaging studies. Admission to an intensive care unit for close cardiorespiratory monitoring should be considered for the child with a mediastinal mass. Similarly, patients with significant electrolyte disturbances due to TLS and those with DIC most likely will require management in an intensive care setting. It may also be appropriate for certain children with suspected leukemia to be admitted to the general pediatric service initially. It is important to recognize that it can be difficult for a family to be admitted to a cancer unit, and this should be done only when the diagnosis is fairly certain. The appropriate setting for further diagnostic

workup and initiation of therapy should be determined in consultation with a pediatric oncologist.

Lymphoma

Lymphomas as a group are the third most common type of cancer in children.²⁰ Timely diagnosis and initiation of appropriate treatment of childhood lymphoma are critical for the following reasons: (1) treatment of childhood lymphoma is effective, and most children with lymphoma have a good chance of long-term survival with appropriate care; and (2) the initial manifestations of lymphoma in children can be life-threatening and often constitute medical emergencies.

Hodgkin lymphoma is the most common type of lymphoma in children and is the most common malignancy in adolescents (age 15–19 years).¹ The remaining histologic types of lymphoma (Burkitt lymphoma, precursor T or B cell lymphoblastic lymphoma, diffuse large B cell lymphoma, and anaplastic large cell lymphoma) are typically lumped together in the category of non-Hodgkin lymphoma (NHL). NHL is more common in younger children than Hodgkin lymphoma, although lymphoma, in general, is rare in children less 5 years of age.²⁰

Common presenting features of lymphoma are listed in **Table 1**. The most common sign of lymphoma in children is enlarging adenopathy. However, most instances of enlarged peripheral nodes in children will be due to causes other than lymphoma. Infection is the most common cause of localized or generalized lymphadenopathy.²¹ Nonetheless, certain characteristics of the patient's adenopathy as well as particular concomitant signs and symptoms should raise concern for possible malignancy.

Most patients with Hodgkin lymphoma and lymphoblastic lymphoma present with some degree of cervical or supraclavicular adenopathy or mass. Intrathoracic masses in the anterior mediastinum, often with pleural effusions, are also common with Hodgkin and non-Hodgkin lymphoma. The most common presentation of children with Burkitt lymphoma in the United States is a large, rapidly growing abdominal mass, often with ascites or pleural effusions. Anaplastic large cell lymphoma and diffuse large B cell lymphoma can occur in a variety of sites and have heterogeneous presentations.

The initial history in children who are diagnosed with lymphoma usually reveals some degree of painless lymphadenopathy. Pain and tenderness, which are uncommon at presentation of lymphoma, are suggestive of a bacterial infection. The onset of adenopathy can vary from months for Hodgkin lymphoma to a few days for Burkitt lymphoma or lymphoblastic lymphoma. Rapidly enlarging nodes, those which become confluent to form a mass, and those that do not respond to antibiotics are concerning for malignancy. In addition, adenopathy or mass in the supraclavicular region always requires further evaluation for possible lymphoma.

Although systemic signs and symptoms are often present, lack of constitutional symptoms does not rule out lymphoma. Fever, fatigue, and weight loss are constitutional symptoms that frequently occur with Hodgkin and non-Hodgkin lymphoma. Approximately one third of patients with Hodgkin lymphoma have specific constitutional symptoms that portend a worse prognosis.²² These so-called "B" symptoms include intermittent unexplained high fevers, unintended weight loss of more than 10% within the previous 6 months and drenching night sweats. Generalized pruritis is a peculiar symptom associated with Hodgkin lymphoma.²³

Physical examination in patients with suspected lymphoma should include palpation of all sites of possible nodal involvement, including the neck, axilla, and groin. Absence of erythema, induration, or tenderness can differentiate a lymphomatous mass from lymphadenitis. Lymph nodes involved with lymphoma are typically firm on palpation and may coalesce into a mass. Abdominal examination may reveal organomegaly

due to lymphomatous infiltration of the liver, spleen, or kidneys. A large mass, distended abdomen, and ascites are common findings with Burkitt lymphoma. A testicular examination in boys is essential because, for unclear reasons, the testicles are sanctuary sites for leukemia and lymphoma cells. This is believed to be due to hematogenous spread rather than spread from the abdomen. A thorough evaluation of respiratory status is critical. Respiratory symptoms associated with lymphoma are usually due to intrathoracic involvement with an anterior mediastinal mass (**Fig. 3**). Symptoms commonly include nonproductive cough, wheezing, dyspnea, and orthopnea. Because it is otherwise rare in children, a history of orthopnea is highly suggestive of a mediastinal mass. Signs of tachypnea, increased work of breathing, wheezing, or hypoxia on examination of a patient with suspected lymphoma should prompt extremely close observation, and further evaluation should be expedited. Superior vena cava (SVC) syndrome may be present in a child with a mediastinal mass. Facial swelling, plethora, cyanosis, and distended neck veins are signs of SVC syndrome. Dyspnea, orthopnea, or signs of SVC syndrome in a child with a mediastinal mass constitutes a medical emergency. The most important aspect of managing a child with a mediastinal mass is to quickly make a diagnosis and initiate cancer-directed therapy while avoiding or at least minimizing sedation. The least invasive procedure that will reveal the diagnosis should be performed. General anesthesia and resultant bronchial smooth muscle relaxation can significantly worsen airway compression and should be avoided.²⁴ A mediastinal mass may result in moderate to severe tracheal or bronchial compression that may require up to 48 hours of IV methylprednisolone (50 mg/m²/day, divided 4 times daily) or dexamethasone (1.5 mg/kg/day, divided 3 times daily)¹³ before any diagnostic procedure is performed. Immediate referral to a pediatric oncologist to direct the diagnostic approach is critical.

Initial laboratory evaluation in a patient with suspected lymphoma should include a complete blood count with manual white blood cell differential. Common childhood lymphomas often present with bone marrow involvement at diagnosis, which may lead to abnormalities in peripheral blood counts as well as lymphoma “blasts” on peripheral blood smear. Serum electrolytes, uric acid, and creatinine should be measured to assess for TLS, which can occur with lymphoblastic and Burkitt lymphomas. Any child with suspected lymphoma should undergo a chest radiograph to evaluate for the presence of a mediastinal mass. Further evaluations, including CT scans, bone marrow

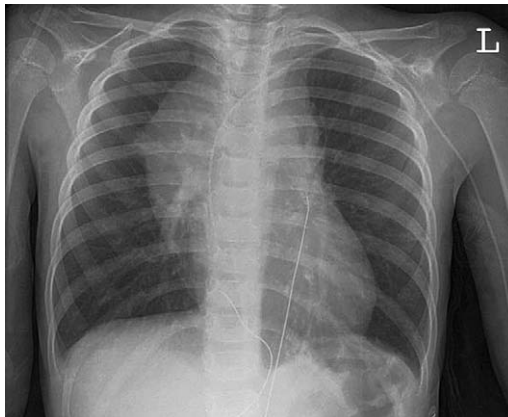


Fig. 3. Chest radiograph of a child with a mediastinal mass.

aspirate/biopsy, thoracentesis or biopsy of adenopathy/mass should be directed by a pediatric oncologist.

SOLID TUMORS

Abdominal Tumors

The most common malignant abdominal tumors in children typically occur before the age of 5 years. Renal tumors and neuroblastoma are the most frequently diagnosed cancers arising in the abdomen. Wilms tumor is the most common tumor of the kidney in children and accounts for 4% of all childhood cancers.¹ There is a clear association between the incidence of Wilms tumor and certain congenital anomalies including aniridia, cryptorchidism, hypospadias, and hemihypertrophy. Children with Beckwith-Wiedemann syndrome, an overgrowth syndrome characterized by macroglossia, organomegaly, and neonatal hypoglycemia, have an 800-fold increased risk of developing Wilms tumor by the age of 4 years.²⁵

Neuroblastoma is the most common extracranial solid tumor diagnosed in children. Neuroblastoma is a cancer of neural crest origin and can arise in the adrenal gland or as a paraspinal mass anywhere along the sympathetic chain. Two thirds of primary neuroblastoma tumors occur in the abdomen.²⁶ As with Wilms tumor, neuroblastoma is typically a disease of young children with 90% of cases diagnosed in children less than 5 years of age.²⁷

Other malignant tumors that may present as abdominal masses in children include primary liver tumors (most commonly hepatoblastoma), non-Hodgkin lymphoma and germ cell tumors involving the ovary or sacrococcygeal region. Rarely, primary sarcomas can occur in the abdomen. Burkitt lymphoma often presents as a rapidly growing abdominal mass, often associated with fever, ascites, and metabolic abnormalities resulting from tumor lysis syndrome. A variety of benign processes such as ovarian cysts, hydronephrosis, multicystic or polycystic kidneys, and mesoblastic nephroma also present as abdominal masses.

The most common presentation of Wilms tumor is the incidental discovery of a palpable abdominal mass by parents, caregivers, or primary care providers on routine examination. Other than the abdominal mass, most children with Wilms tumor are asymptomatic. Pain with the mass can occur, but is not a typical feature. Often a history of trauma is present, which may have alerted the parents or physician to notice the mass. Hematuria and hypertension may also be present at diagnosis.

Although neuroblastoma may also present as a painless abdominal mass, constitutional symptoms often occur due to a high prevalence of metastatic disease at diagnosis. More than 50% of cases of neuroblastoma are metastatic at diagnosis; the most common sites of metastasis are bone, bone marrow, and liver.²⁷ Bone pain, fever, weight loss, and irritability are common presenting symptoms of metastatic neuroblastoma. Infants with so-called stage 4S neuroblastoma may have skin involvement with green/blue colored palpable cutaneous nodules. Neuroblastoma is a catecholamine-secreting tumor and therefore occasionally results in hypertension, tachycardia, flushing, and diarrhea. Opsoclonus-myoclonus is a rare syndrome, characterized by dancing eye movements, ataxia, and myoclonic jerks, and it occurs in 2% to 3% of children diagnosed with neuroblastoma.²⁸

Physical examination of a child with a suspected abdominal mass should include assessment of vital signs including blood pressure. Abdominal examination may help to determine the location of origin, although this is sometimes not possible with large masses. For patients with Wilms tumor, a large firm flank mass may be the only abnormal finding on examination. Children with neuroblastoma may appear ill and are often irritable. Additional signs may be seen with metastatic disease to

bone. Periorbital ecchymoses and proptosis are classic signs due to metastatic involvement of periorbital bones (**Fig. 4**). Patients with suspected neuroblastoma require a thorough neurologic examination. Tumors that arise from sympathetic ganglia can invade through neural foramina resulting in cord compression. Lower extremity weakness or paralysis in a child with suspected malignancy is a medical emergency necessitating immediate evaluation and intervention. A child presenting with spinal cord compression requires emergent consultation with neurosurgery and radiation oncology services.

Initial laboratory evaluation may be helpful in narrowing the differential diagnosis in a patient with an abdominal mass. Leukopenia, anemia, or thrombocytopenia on a complete blood count can be due to bone marrow involvement of neuroblastoma or lymphoma. Serum chemistries should be obtained to assess renal function and evaluate for tumor lysis syndrome. Children with abdominal Burkitt lymphoma often present with elevated uric acid, hyperphosphatemia, and hyperkalemia resulting from TLS. Homovanillic acid (HVA) and vanillylmandelic acid (VMA) are catecholamine metabolites that are highly sensitive and specific for neuroblastoma if detected in spot urine samples.

Abdominal ultrasound is a useful initial radiographic test for evaluation of a suspected abdominal mass. Ultrasound can often determine the origin of the mass as well as the density of the mass. Lesions that are cystic or fluid-filled can be differentiated from solid masses by ultrasound. However, thorough delineation of an abdominal mass is better accomplished by CT scan, which is generally the imaging modality of choice for abdominal tumors (**Fig. 5**). Paraspinal masses necessitate an MRI scan to assess for extension into neuroforamina and possible spinal cord impingement.

Bone and Soft-tissue Tumors (Musculoskeletal Tumors)

Bone and soft-tissue tumors account for approximately 12% of childhood cancer diagnoses.¹ Osteosarcoma and Ewing sarcoma are the most common malignant bone tumors in children and adolescents. Rhabdomyosarcoma is the most common soft-tissue tumor in children.

Malignant bone tumors typically occur in the second decade of life, and are often discovered around the time of the adolescent growth spurt. In contrast to osteosarcoma, Ewing sarcoma is sometimes diagnosed in young children and infants.



Fig. 4. 13-month-old child with neuroblastoma presenting with periorbital ecchymoses.

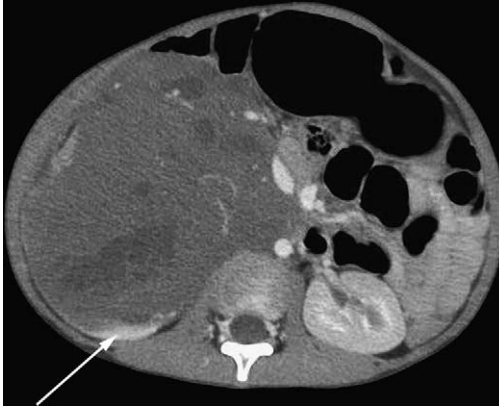


Fig. 5. CT scan of a Wilms tumor. The picture shows a large retroperitoneal mass arising from the right kidney. The arrow points to a remnant of renal tissue.

Osteosarcoma most often develops in the metaphyseal portion of long bones; the distal femur, proximal tibia, and proximal humerus are the most common sites. In contrast, Ewing sarcoma tumors frequently arise from flat bones or from the diaphyseal portion of long bones. Approximately one fourth of Ewing sarcoma tumors arise in the pelvis, which is the most common site of involvement.²⁹

Pain with or without swelling at the involved site is the most common presenting symptom in patients diagnosed with bone tumors.²⁹ The pain may be intermittent initially, but typically becomes more constant and more severe over time. It is not uncommon to have a delay of several months from onset of symptoms to diagnosis of a bone tumor. The presenting signs and symptoms of bone tumors can often be difficult to distinguish from those caused by trauma. Patients eventually diagnosed with bone tumors are often initially treated for presumed sports injuries with rest, ice, and antiinflammatory medication. However, injury-associated pain usually gets better with rest, whereas pain due to malignant bone tumor does not remit and progressively worsens over time. Bone tumor pain is also sometimes mistaken for “growing pains.” However, pain that is severe enough to wake a child or adolescent from sleep deserves further evaluation. A malignant bone tumor should also be suspected with any fracture that occurs in an unusual site or after seemingly minor trauma. This type of bone injury is often described as a “pathologic fracture.”

The initial evaluation of patients with suspected bone tumors should include a thorough history and physical examination. Osteosarcoma is sometimes associated with familial cancer syndromes such as hereditary retinoblastoma and Li-Fraumeni syndrome and may occur as a secondary malignancy in patients who previously received radiation therapy. A history of fever, weight loss, or night sweats should alert the physician to the possibility of cancer, although patients with bone tumors often have no symptoms other than pain. Physical examination reveals tenderness at the involved site, and there is often a palpable soft-tissue mass. Radiographs of the involved bone are the best initial radiographic study. Plain radiographs typically show a destructive lesion in the involved bone with disruption of the cortex (Fig. 6). A classic radiographic finding with malignant bone tumors known as “Codman triangle” results from elevation and detachment of periosteum from bone. A soft-tissue mass is often present with osteosarcoma or Ewing sarcoma. Location of the lesion (metaphysis versus diaphysis) may raise suspicion of a particular type of



Fig. 6. Lateral view plain radiograph of osteosarcoma of the distal femur.

bone tumor (Ewing sarcoma or osteosarcoma, respectively), but biopsy is the definitive way to make this distinction. Patients with suspected malignant bone tumors should be referred to a pediatric oncologist or orthopedic oncologist as the patient will require further imaging studies and biopsy of the mass. The differential diagnosis includes osteomyelitis, benign tumors and cysts of bone, and rheumatologic disorders. Children with acute leukemia can also present with bone pain and a limp.

Soft-tissue sarcomas can occur at any site, and children diagnosed with a soft-tissue sarcoma usually present with painless masses. Approximately 900 new cases of soft-tissue sarcoma are diagnosed in the United States each year.¹ These tumors are more common in children with the following familial cancer predisposition syndromes: Li-Fraumeni, neurofibromatosis type 1 and Gardner syndromes.

Rhabdomyosarcoma is the most common soft-tissue sarcoma in children. Two thirds of rhabdomyosarcomas are diagnosed in children less than 6 years of age.³⁰ Common sites of involvement include the head and neck region (orbit, nasopharynx, sinuses, and superficial face), the genitourinary tract (bladder, vagina, and testis), extremities, and the trunk including retroperitoneum. Adolescents with rhabdomyosarcoma are more likely to have tumors of the extremities. Although rhabdomyosarcoma is a tumor of primitive skeletal muscle cells, it can occur in sites in the body that do not normally contain skeletal muscle.

Initial evaluation depends on the site of involvement. Tumors of the head and neck arising in parameningeal sites may present with signs of nasal obstruction, decreased smell or hearing, and cranial nerve palsies. Ptosis and proptosis are common manifestations of orbital rhabdomyosarcoma (Fig. 7). Hematuria or urinary retention may be the presenting symptoms of tumors arising in the bladder. Vaginal rhabdomyosarcoma often presents with bloody mucoid discharge in young girls before a mass is seen. Paratesticular tumors are usually painless and can be mistaken for hydroceles. Rhabdomyosarcoma involving extremities occurs with higher frequency in adolescents and is more commonly associated with regional or distant metastases at diagnosis.

After a thorough history and physical examination, imaging of the primary site is indicated. Plain radiographs may be helpful to evaluate for bone involvement. Either CT scan or MRI of the involved site is the most effective means to assess tumor extent.

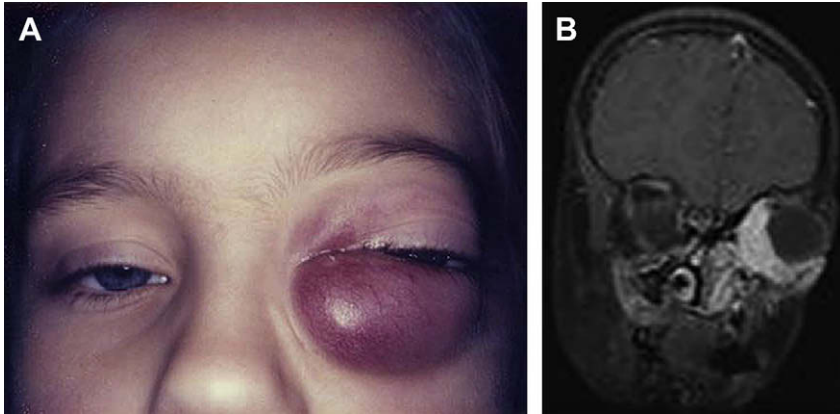


Fig. 7. Photograph (A) and coronal MRI image (B) of a child with orbital rhabdomyosarcoma.

Although a differential diagnosis can be formulated based on the radiographic appearance of the lesion, tissue by either excisional or incisional biopsy is required for definitive diagnosis. Suspicion of cancer should prompt immediate consultation with a pediatric oncologist.

Soft-tissue sarcomas other than rhabdomyosarcoma are a heterogeneous group of cancers with a variety of histologic subtypes. These tumors typically arise in the extremities and trunk, and unlike rhabdomyosarcoma, are unusual in the head and neck. Nonrhabdomyosarcomatous soft-tissue sarcoma (NRSTS) usually presents as a painless mass. As this category of tumors encompasses a variety of histologic subtypes from low to high grade, the rate of growth can vary significantly from patient to patient. NRSTS can occur as secondary malignancies within a field of prior radiation in patients previously treated for cancer. Imaging of the involved site is the appropriate next step after history and physical examination in a patient with suspected soft-tissue sarcoma. Biopsy is necessary to make a histologic diagnosis and distinguish a sarcomatous lesion from a benign growth.

SUMMARY

The role of the ED physician in the recognition and initial management of a child with a new diagnosis of cancer is an important one. Although the signs and symptoms of these patients can be vague and can mimic other more common childhood illnesses, there are often specific elements of the cancer patient's history, examination, and laboratory evaluation that can lead the provider to the correct diagnosis. Particular attention should be paid to the patient who makes repeated visits for a persistent complaint that has not been fully evaluated. Although many strides have been made in the treatment of childhood cancers, even the most curable malignancies can be life-threatening at the time of diagnosis. Appropriate and timely initial management by the ED provider is often the first step to a good outcome for a child diagnosed with cancer.

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REFERENCES

1. Li J, Thompson TD, Miller JW, et al. Cancer incidence among children and adolescents in the United States, 2001–2003. *Pediatrics* 2008;121:e1470–7.
2. Linet MS, Ries LA, Smith MA, et al. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *J Natl Cancer Inst* 1999;91:1051–8.
3. Miller LC, Sisson BA, Tucker LB, et al. Prolonged fevers of unknown origin in children: patterns of presentation and outcome. *J Pediatr* 1996;129:419–23.
4. Gurney JC, Smith MA, Bunin GR. CNS and miscellaneous intracranial and intraspinal neoplasms. SEER Pediatric Monograph. In: Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR, editors. *Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995*. Bethesda (MD): National Cancer Institute; 1999. SEER Program. NIH Pub.No. 99–4649:51–63.
5. Gurney JG, Kadan-Lottick N. Brain and other central nervous system tumors: rates, trends, and epidemiology. *Curr Opin Oncol* 2001;13:160–6.
6. Blaney SM, Kun LE, Hunter J, et al. Tumors of the Central Nervous System. In: Pizzo PA, Poplack DG, editors. *Principles and practice of pediatric oncology*; 2006. p. 786–864.
7. Lewis DW. Headaches in children and adolescents. *Curr Probl Pediatr Adolesc Health Care* 2007;37:207–46.
8. Anonymous. The epidemiology of headache among children with brain tumor. Headache in children with brain tumors. The childhood brain tumor consortium. *J Neurooncol* 1991;10:31–46.
9. Wilne SH, Ferris RC, Nathwani A, et al. The presenting features of brain tumours: a review of 200 cases. *Arch Dis Child* 2006;91:502–6.
10. Wilne S, Collier J, Kennedy C, et al. Presentation of childhood CNS tumours: a systematic review and meta-analysis. *Lancet Oncol* 2007;8:685–95.
11. Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. *Neurology* 2000;55:616–23.
12. Lewis DW, Packer RJ, Raney B, et al. Incidence, presentation, and outcome of spinal cord disease in children with systemic cancer. *Pediatrics* 1986;78:438–43.
13. Rheingold SR, Lange BJ. Oncologic emergencies. In: Pizzo PA, Poplack DG, editors. *Principles and practice of pediatric oncology*. 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 1202–30.
14. Albano EA, Sandler E. Oncologic emergencies. In: Altman AJ, editor. *Supportive care of children with cancer*. 3rd edition. Baltimore: Johns Hopkins University Press; 2004. p. 221–42.
15. Smith MA, Gloeckler-Ries LA, Gurney JG. Leukemia. In: Ries LAG, Smith MA, Gurney JG, editors. *Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995*. Bethesda (MD): NCI, SEER Program NIH Pub; 1999. p. 17–34.
16. Pui CH. Acute lymphoblastic leukemia in children. *Curr Opin Oncol* 2000;12:3–12.
17. Swensen AR, Ross JA, Severson RK, et al. The age peak in childhood acute lymphoblastic leukemia: exploring the potential relationship with socioeconomic status. *Cancer* 1997;79:2045–51.

18. Margolin JF, Steuber CP, Poplack DG. Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 5th edition. Philadelphia: Principles and practice of pediatric oncology; 2006. p. 538–90.
19. Baranski B, Young N. Hematologic consequences of viral infections. *Hematol Oncol Clin North Am* 1987;1:167–83.
20. Link MP, Weinstein HJ. Malignant non-Hodgkin lymphomas in children. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 722–47.
21. Twist CJ, Link MP. Assessment of lymphadenopathy in children. *Pediatr Clin North Am* 2002;49:1009–25.
22. Raney RB. Hodgkin's disease in childhood: a review. *J Pediatr Hematol Oncol* 1997;19:502–9.
23. Hudson MM, Onciu M, Donaldson SD. Hodgkin lymphoma. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 695–721.
24. Goh MH, Liu XY, Goh YS. Anterior mediastinal masses: an anaesthetic challenge. *Anaesthesia* 1999;54:670–4.
25. DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. *J Pediatr* 1998;132:398–400.
26. Brodeur GM, Maris JM: Neuroblastoma. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology, 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 933–70.
27. Haase GM, Perez C, Atkinson JB. Current aspects of biology, risk assessment, and treatment of neuroblastoma. *Semin Surg Oncol* 1999;16:91–104.
28. Matthay KK. Neuroblastoma: a clinical challenge and biologic puzzle. *CA Cancer J Clin* 1995;45:179–92.
29. Arndt CA, Crist WM. Common musculoskeletal tumors of childhood and adolescence. *N Engl J Med* 1999;341:342–52.
30. Dagher R, Helman L. Rhabdomyosarcoma: an overview. *Oncologist* 1999;4:34–44.