

# Emergency Presentations of Cancer in Childhood

Richard M. Ruddy, MD

Childhood cancer is an important area for pediatricians and emergency physicians to have an up-to-date knowledge based on both diagnostic and therapeutic issues. Clinical cases of some common childhood cancers will be presented as the basis for the review of how these potentially lethal disorders can present. Patient assessment and initial workup and pertinent components of the differential diagnosis will be discussed. With a growing number of children successfully treated for cancer, long-term care-related issues are also reviewed. Childhood leukemia, neuroblastoma and Wilms tumor will be reviewed in more depth. The goal of this paper is to guide the reader in these relatively uncommon, although extremely important, clinical presentations of cancer in children.

Clin Ped Emerg Med 6:184-191 © 2005 Published by Elsevier Inc.

**KEYWORDS** Childhood cancer, Leukemia, Wilm's tumor, Neuroblastoma

Childhood cancer is an important clinical entity to be prepared for in both office and emergency department settings. Approximately 1 in 7000 children younger than 14 years will be diagnosed with childhood cancer each year [1]. When extrapolated to age 20, more than 12000 children a year are diagnosed with cancer, most of these in children younger than 15 years. Table 1 contains a list of selected cancers and their respective frequency and sex distributions [1]. Cancer is the number 2 killer of children after injuries and is the number 1 medical cause of death after 1 year of age. Because of therapeutic advances achieved over the past 10 to 15 years, many of the childhood cancers have undergone substantial improvement in their outcomes. Improved outcomes aside, there still remains a significant ongoing impact on both the child and family, requiring involvement of health care providers at both the tertiary medical center as well as at the community level. Illustrative cases will be presented to give the reader an overview of key clinical issues with several pediatric cancers.

## Case 1

An 8-month-old male infant presents to the office with a 2-week history of low-grade fever. The infant's mother describes an intermittent fever 101°F to 102°F, with little prodrome or evidence of a specific infectious process.

There is no vomiting or diarrhea reported, and there is no cough, congestion, or rash. The child's appetite is off a bit, but he is still drinking reasonably well and has not visibly lost weight. The patient's 3-year-old sibling has been well except for an upper respiratory tract infection with fever a few weeks earlier. The patient has had all of his immunizations and had an ear infection and bronchiolitis in the winter. He is on no medications, except intermittent ibuprofen.

On physical examination, the infant is alert and non-toxic appearing. His vital signs note a heart rate of 132 beats per minute, respiratory rate of 52 breaths per minute, and a temperature of 38.3°C (100.9°F). Examination of the head reveals dull but mobile tympanic membranes, a normal oropharynx, and small nontender anterior cervical nodes. His neck is supple. Examination of the chest notes no crackles, wheezes, or rhonchi. The cardiovascular examination demonstrates good pulses and capillary refill with normal heart sounds. Palpation

Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH.

Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Reprint requests and correspondence: Richard M. Ruddy, MD, Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229.

**Table 1** Incidence of cancer by sex in children 0 to 14 years in the United States.

Diagnosis	Rate (per 1 000 000)	Male/Female Ratio
Total	141.3	1.2
ALL	32.4	1.2
AML	6.6	1.0
Hodgkin disease	5.7	1.1
Non-Hodgkin lymphoma	8.5	2.5
CNS tumor	31.8	1.2
Neuroblastoma	10.1	1.2
Wilms tumor	7.9	1.0
Malignant bone tumors	7.0	1.2
Rhabdomyosarcoma	5.1	1.3
Retinoblastoma	4.0	0.9

Adapted from Smith and Gloeckler Ries [11].

of the abdomen reveals no organomegaly or masses. The infant's extremities, neurological examination, and genitalia are all normal. Examination of the skin demonstrates no rash, petechiae, or purpura.

From your clinical experience, what findings are important in your assessment of this child? First, your fairly detailed history and physical examination really did not reveal more than a fever that has lasted significantly longer than what is typical for a viral infection. There are no specific physical findings to help you come to a particular infectious disease as the cause of the current illness. Although it may be true that there was no consistent fever every day, it appears that this illness has lasted 2 full weeks. A urinary tract infection should be considered, although making that less likely are that this is a circumcised male infant, older than 6 months, with only persistent low-grade fever. Pneumonia is a possibility, but again, the absence of respiratory symptoms does not make the pretest probability of a chest radiograph very high. Thus, your differential diagnosis migrates from things that have fever as the sole manifestation and with less than 5 to 7 days of duration to other entities. Pizzo et al [2] reviewed cases of fever greater than 38.5°C for 2 weeks' duration in 100 children. In the 52 children younger than 6 years, 34 had infectious disease diagnoses, 4 had a collagen vascular disease, and 4 had an underlying malignancy. The older children in this study had a much higher incidence of collagen vascular disease in the causative diagnoses. Although this is "old" literature (1975), even predating the recognition of Kawasaki disease, your differential diagnosis would still have you consider similar causes of fever of unknown origin with both atypical presentations of common and more unusual infections, occult cancer, and rheumatologic disease. Should you take that path with diagnostic testing?

After having a brief discussion with the infant's mother in the office, you elect to obtain a few tests to help determine the next steps—a complete blood count

(CBC), chest radiograph, and a urinalysis and culture. You will obtain the results and call the family at the end of the day to decide how to next proceed unless there are results that surprise you. The infant's urine is normal with no white blood cells (WBCs) or protein. There were also no abnormalities seen in the chest radiograph. The CBC reveals a hemoglobin of 9.2 g/dL, hematocrit of 26.9, platelet count of  $156 \times 10^9/L$ , and a WBC count of  $12.6 \times 10^9/L$  with a differential of 88% lymphocytes, 8% neutrophils, 2% band forms, and 2% monocytes. You make a phone call.

## Case 2

A 3.5-year-old girl with foot pain for a week and limp comes to the office for an evaluation. Her mother noted no specific trauma, and the child has had no intercurrent illness or fever.

Physical examination reveals an alert non-ill-appearing child who is notably pale. Vital signs include a heart rate of 96 beats per minute, respiratory rate of 20 breaths per minute, and a temperature of 36.2°C (97.2°F). Examination of the head and neck reveals shotty cervical lymphadenopathy. Examination of the chest and the cardiovascular system are normal. Palpation of the abdomen reveals no organomegaly or masses. Extremity examination reveals her left distal shin to be slightly swollen laterally with tenderness to palpation. There are no rashes or bruises found.

An extremity radiograph (Figure 1) and laboratory workup are obtained at the community hospital. The CBC reveals a hemoglobin of 7.8 g/dL, hematocrit of 22%, platelet count of  $113 \times 10^9/L$ , and WBC count of



**Figure 1** Distal tibia and fibula radiograph demonstrating "moth-eaten" appearance to the fibula.

$4.2 \times 10^9/L$  with 95% lymphocytes and 5% atypical lymphocytes. No blasts were seen on the peripheral smear. You refer this patient to the hospitalist for evaluation and admission through the emergency department, discussing your findings and concerns about cancer and infection as possible causes.

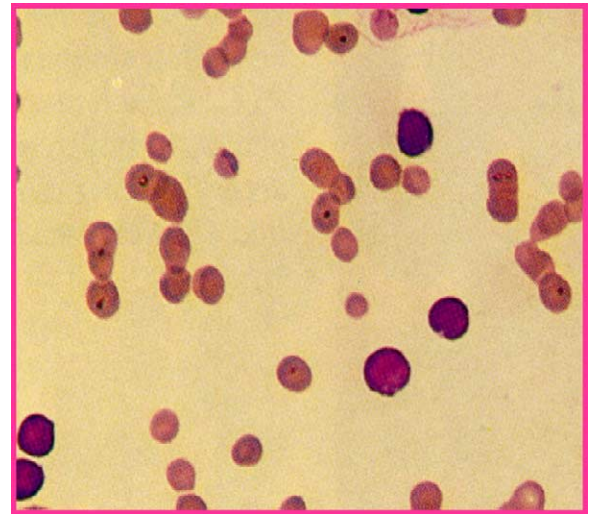
## Discussion

Both of these cases are somewhat atypical presentations of acute lymphocytic leukemia (ALL). The first case illustrates the workup of a child with fever of unknown origin (a prolonged fever), and the second case discusses a child with subtle findings on physical examination (pallor from anemia) and focal bony abnormalities. In the first case, your phone call is to a pediatric hematologist/oncologist to request a review of the smear, who then makes the diagnosis when peripheral lymphoblasts are seen. The girl with limp really has 2 entities in the differential diagnosis from her radiograph, leukemia and Ewing sarcoma. Other considerations on the differential diagnosis in many similar presentations might include aplastic anemia, some of the rheumatologic diseases such as juvenile rheumatoid arthritis or systemic lupus erythematosus, idiopathic thrombocytopenic purpura, infectious mononucleosis, and other solid tumors such as rhabdomyosarcoma or neuroblastoma. The clinical findings often associated with newly diagnosed ALL include those listed in Table 2. Typically, one looks for a young child with fever and fatigue, generalized lymphadenopathy, hepatosplenomegaly, and bruising. In such a patient with a more typical presentation, we expect to see or hear from the laboratory that there are lymphoblasts on the peripheral smear.

Both cases reveal that the classic triad of peripheral blood count abnormalities in red blood cells (anemia), platelets (thrombocytopenia), and white cells (peripheral blasts) may not be present or sufficiently abnormal for a diagnosis at presentation. Red blood cells are most often reduced in count because of the marrow predominantly filled with lymphoblasts. This anemia is commonly normochromic and normocytic. On occasion, nucleated red blood cells are apparent from bone marrow invasion leading to nucleated red blood cells being released from the packed marrow. Platelets are often less than

**Table 2** Findings in ALL.

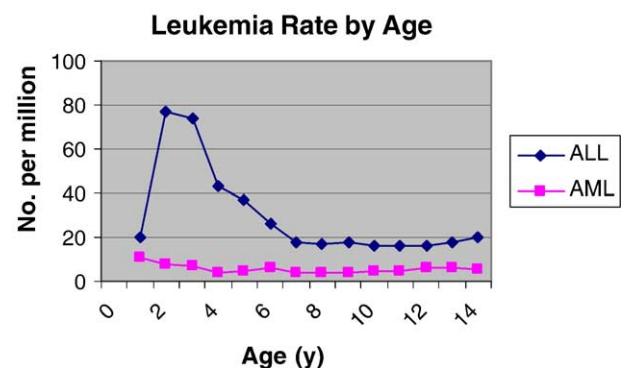
- Symptoms—pallor, fatigue and irritability, bleeding (usually bruising or epistaxis), fever
- Signs—pallor, bruising, weakness, hepatosplenomegaly (30%-50%), and adenopathy
- Laboratory workup—anemia, thrombocytopenia, and abnormal WBCs (approximately 50% present with WBC  $<10 \times 10^9/L$  and approximately 20% present with WBC  $>50 \times 10^9/L$ )
- CXR—mediastinal mass (5%)



**Figure 2** Peripheral blood smear demonstrating lymphoblasts, normal and nucleated red blood cells, and absence of visible platelets.

$100 \times 10^9/L$  at presentation but usually are normal in appearance. Leukocytes on peripheral counts vary greatly from low counts, often without blasts visualized, to counts more than  $100 \times 10^9/L$ . In immediate management, it is important to understand that with high WBC counts, significant complications can occur from the impact this has on the microcirculation. Figure 2 shows a typical slide of a patient with ALL, who has blasts, nucleated red blood cells, and no visible platelets on the smear. The diagnosis of leukemia is sometimes made and always confirmed by review of bone marrow aspiration or biopsy, examinations typically demonstrating a hypercellular marrow with at least 25% blasts. Variations in the findings at different marrow locations or fibrosis at a biopsy site may require more than one marrow aspirate or a biopsy to confirm the diagnosis.

Leukemia accounts for almost one third of childhood cancer, and ALL, in most studies, represents 75% of the diagnoses [3,4]. Acute myeloid leukemia (AML) accounts for 15% to 20% of childhood leukemia. The age and race



**Figure 3** Age incidence rate (per million population) of ALL and AML in children. Adapted from Gurney et al [5].

distribution for ALL and AML is shown in Figure 3 [5]. As noted in the Figure, there is an incidence peak for ALL at age 2 years and an early peak in infancy for AML. Not demonstrated is the higher rate of ALL in whites versus blacks in the United States throughout childhood.

Leukemia risk factors have been investigated at some length [3]. Genetic factors are associated with increases in leukemia rates. This includes conditions such as Down syndrome (trisomy 21), neurofibromatosis type I, and other conditions associated with chromosome breakage. There is clearly an increased statistical risk with environmental in utero exposure to radiation, but reported risks range from 1.1 to 2.0. After the atomic bomb detonations in Japan, there was an increased rate of leukemia in children years after exposure. This phenomenon was not demonstrated after other potential radiation exposures such as Chernobyl. There continues to be a great deal of controversy regarding this, but clearly, the actual risk is still quite small to most children. Repeated exposure to electromagnetic radiation has been well studied in recent years, but to date, epidemiological data do not substantiate any relationship between electromagnetic radiation and leukemia.

Although an in-depth discussion of the prognostic features that have been shown to be significant for leukemia is often important early on in the discussion with a family, it is often not part of the “breaking the bad news” by the family physician, pediatrician, or emergency physician. The 2 most obvious prognostic findings are the child’s age at presentation and the initial WBC count. Infants younger than 1 year, especially those who present with high WBC counts and a specific chromosomal rearrangement (MLL gene on chromosome 11q23), and adolescents (>10 years) have a less favorable prognosis [6]. Children presenting with a WBC count greater than  $50 \times 10^9/L$  also have a less favorable prognosis. The other features used to classify patients include immunophenotyping, chromosomal abnormalities, and presence of lymphoblasts in the cerebrospinal fluid at diagnosis. It is important that this testing be part of the pretreatment diagnostic workup.

Treatment under the direction of a pediatric oncologist should begin immediately. Outcomes have improved greatly, with 95% of patients entering clinical remission during induction and more than 80% remaining disease-free on long-term follow-up [4,6]. Initial therapy is directed at minimizing the risk of hematologic problems associated with thrombocytopenia and anemia, infectious complications of neutropenia, and the metabolic issues that can occur during induction. Induction routinely involves at least 3 drugs; 2 of which are prednisone and vincristine, often with L-asparaginase or anthracycline. Some protocols call for more intensive therapy based on clinical presentation and prognostic grouping. Lumbar puncture is performed at initiation of therapy for evaluation of central nervous system (CNS) involvement

and is often used for intrathecal chemotherapy administration at that time. Intensification therapy is standard after remission is induced (or after a short interval) and is followed by continuation or maintenance therapy for up to a total of 2 or more years. During any of the 3 intervals, it is common for the primary care physician or emergency physician to have clinical contact with these children, particularly over issues related to granulocytopenia and fever, often in a child with an indwelling central line.

Therapies to reduce the risk of complications are important to initiate early, along with the start of cancer therapy. The presence of moderate to severe anemia at presentation is a reason for red blood cell transfusion, with experts recommending a minimum hematocrit of 0.20 to 0.25 at the start of therapy. Similarly, although based on expert opinion, platelet transfusions should be strongly considered when the platelet count is less than  $15$  to  $20 \times 10^9/L$  even in the absence of significant clinical bleeding. Although rare, disseminated intravascular coagulopathy may require treatment in some patients upon presentation with leukemia. Although not commonly manifested at diagnosis, bacterial infection may be present in a patient with leukemia, in part due to granulocytopenia, which will require diagnosis and antimicrobial therapy. Another relatively uncommon but serious complication during neutropenia is typhlitis, a syndrome of right-sided abdominal pain, vomiting, and sepsis associated with intensive chemotherapy and prolonged neutropenia. Typhlitis can lead the clinician to perform diagnostic testing, which may cause delay in administration of therapy for sepsis including aggressive intravenous (IV) fluid administration and broad-spectrum antibiotics. At the onset of induction chemotherapy, it is also important to initiate allopurinol to prevent the production of uric acid that can occur after lysis of tumor cells, a problem especially in patients with a high tumor burden. It is key to maintain hydration at initiation of induction with IV fluids containing bicarbonate to enhance the formation of alkaline urine. Other important problems occurring in patients with leukemia are acute neurological events, such as seizures from intrathecal therapy, neuropathy from vincristine, and a “somnolence” syndrome from cranial radiation, which can manifest 1 to 2 months later. These treatment complications all tend to be short term but may require therapy and consultation with the oncologist and a neurologist. Lastly, it is important to consider the specific side effects of chemotherapeutic agents that may occur during a child’s treatment—such as the potential complications of long-term corticosteroids on glucose and bone metabolism, blood pressure, and the gastrointestinal tract—and that a small but significant percentage of children on L-asparaginase may develop pancreatitis.

Primary care clinicians and emergency physicians should also be aware that children with a history of leukemia are at significant risk of long-term issues that

**Table 3** Long-term issues with childhood leukemia.

Cardiac toxicity	Anthracycline toxicity
Growth failure	Cranial radiation, corticosteroids
CNS complications	Cranial radiation
Bone mineralization	Corticosteroids
Sexual development and fertility	Radiation, alkylating agents
Solid organ cancer	Radiation
Risk of lymphoproliferative disorder	Chemotherapy
Graft-vs-host disease	Nonradiated blood products or bone marrow transplant

may bring them to the attention of health care providers, as listed in Table 3 [6]. This includes 2 categories of problems—the impact of therapy in achieving a cure and the issues around relapse and secondary cancer. Bone marrow relapse occurs in 20% to 30% of cases and is an important prognostic factor, where early relapse confers a worse prognosis. Much better outcomes after relapse are associated with the opportunity for a sibling-matched allogeneic stem cell transplant during the second remission. This is much more successful than repeated chemotherapy or transplant with unrelated or autologous stem cells.

In summary, the diagnosis and management of acute leukemia in childhood is a challenge that, although uncommon in the general practice of pediatrics, is still important with 3000 new cases diagnosed per year in the United States.

### Case 3

A 2-year-old girl fell off the couch at home today. Her mother noted her to have a swollen abdomen and some tenderness within an hour or so of the fall. She was previously well except for a short febrile illness of 1-week duration, treated with amoxicillin with good response.

Physical examination reveals an uncomfortable girl with a protuberant abdomen. Vital signs include a heart rate of 132 beats per minute, respiratory rate of 28 breaths per minute, blood pressure of 128/72 mm Hg, and a temperature of 37.5°C (99.6°F). Examination of the child's abdomen notes fullness of the left side and flank, which is mildly tender to palpation in the axillary line. The remainder of the child's physical examination is unremarkable, with no abnormalities found.

### Discussion

A child with an abdominal mass should elicit a fairly extensive differential diagnosis (Table 4). The history and physical examination need to exclude other important entities such as trauma, including nonaccidental or inflicted injury, as well as a number of other causes, including infectious diseases. With a low suspicion for

those other conditions, the diagnostic focus will be toward the top 2 on the list in Table 4, the 2 most common intra-abdominal cancers, Wilms tumor and neuroblastoma. Two important and fairly immediate concerns in the evaluation for these entities include careful assessment and reassessment of the blood pressure (it is significantly elevated at 128/72 mm Hg), and an assessment for the spread of the cancer to other sites such as bone, peripheral blood, and so on.

Wilms tumor is an embryonic neoplasm arising from the kidney and is responsible for 6% of childhood cancer [7]. It most frequently presents as an asymptomatic abdominal mass but may present, as was in this patient, as a painful abdominal mass that results from bleeding into the tumor. More than a quarter of the children with Wilms tumor have hypertension, and almost a quarter have fever at presentation. Common features at presentation may include anorexia, vomiting, weight loss, hematuria, and, occasionally, bone pain. Although quite uncommon, children with aniridia (absence of their iris) and hemihypertrophy are at increased risk to have this tumor. The physical examination should include palpation of a flank mass that does not move with respiration. The genitourinary examination should focus on associated findings including hypospadias, cryptorchidism, and even pseudohermaphroditism. The laboratory workup would include a CBC and liver and renal function tests. It is important to measure the serum calcium and phosphate as well as to assess coagulation, because of the association of elevated von Willebrand factor.

Diagnostic imaging may begin with an ultrasound, but computed tomography (CT) is required to fully delineate the mass and involved structures. Figures 4 and 5 shows 2 patients with Wilms tumor on intravenous pyelography and CT. A chest x-ray (CXR) should be obtained to evaluate for the presence of tumors in the chest. Some authors believe that it is important to obtain a chest CT, even if the CXR does not show abnormalities, because CT is more sensitive for small areas of metastasis [8,9]. Some studies have not shown a difference in outcome when the chest film has been negative even with the presence of

**Table 4** Differential diagnosis of abdominal mass.

■ Wilms tumor
■ Neuroblastoma
■ Lymphoma or leukemia with hepatosplenomegaly
■ Hepatomegaly
○ Hepatoblastoma
○ Choledochal cyst
○ Glycogen storage disease
■ Noncancerous renal masses
○ Multicystic or polycystic kidneys
○ Dysplastic kidney
○ Hydronephrosis
■ Others—teratoma, rhabdomyosarcoma, ovarian cysts, mesenteric cysts



**Figure 4** Intravenous pyelogram in a 2-year old with Wilms tumor, showing left-sided mass and distortion of normal calyces.

small nodules on CT, but the evidence is not clear. Diagnosis is best verified at surgical excision or biopsy because there are histological features which impact on outcome prognosis and recurrence risk. The absence of microscopically seen anaplastic changes affords a much better prognosis. It is advisable to refer these children early to a pediatric tertiary center where both surgical and oncological expertise can contribute to care. In the United States, most experts recommend early and, if possible, complete tumor resection, followed by tumor categorization and chemotherapy. Some centers in Europe will first start with chemotherapy and then resect tissue after there has been a reduction in tumor size. The potential disadvantage of this approach is that some patients with a low-risk tumor may undergo unnecessary chemotherapy [8-10]. Tumor staging most generally includes definition of tumor extension and tissue pathology with the presence of anaplasia, representing the most important feature. For patients with more favorable tumor tissue types, they will receive chemotherapy with dactinomycin and vincristine. For patients with stage III or IV disease, doxorubicin and radiation therapy will have to be added. With a combination of surgery and chemotherapy, the cure rate is 80% to 90% in most centers [7].

Children must be regularly followed after the completion of successful treatment with abdominal ultrasound and either CXR or chest CT. Chest CT is the single best study to identify recurrent disease if present; although in patients with a history of disseminated tumor, the disease may have other sites as the location of relapse. Children who have been treated for Wilms tumor have a number of organ systems that may have had

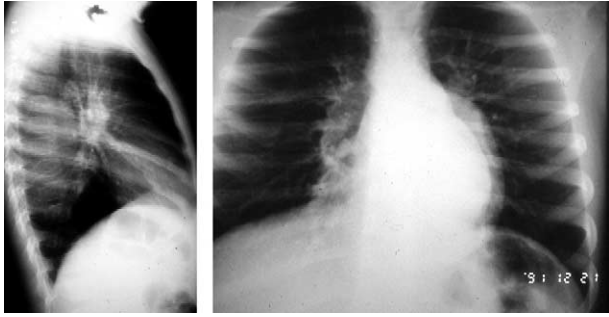
potential treatment complications. Renal function can be diminished, although the incidence of renal failure is low unless there are other issues, including radiation nephritis. Cardiac function can be impaired if the child has been treated with doxorubicin, which can impair left ventricular performance. The impact of radiation on the lungs and the effects of chemotherapy on the liver and the bone marrow also require close follow up. Gonadal function in men and women and fertility are also an issue because of alkylating agents and radiation. In addition, there is a small risk of secondary cancer depending on whether chemotherapy or radiation therapy was used. In summary, although the outcome of children with Wilms tumor is now quite good, there is a need for clinicians to understand the long-term care issues that remain throughout childhood and early adulthood.

The second most prevalent solid tumor presenting at this age is neuroblastoma [11,12]. It accounts for approximately 10% of childhood cancer, making it a relatively common entity. Neuroblastoma is a solid tumor arising from neural crest cells and is typically a centrally located mass (as opposed to the Wilms tumor which is typically lateral as it originates from the kidney). There are 3 histological types presenting with “small, round, blue cells” ranging from well-differentiated ganglioneuroma, to ganglioneuroblastoma, to neuroblastoma. The prognosis is much better in the well-differentiated type of tumor. Approximately two thirds of these tumors come to medical attention as an abdominal mass. The rest arise in the chest and occasionally in the neck. The cervical masses are especially deceptive in that clinicians may consider them as an infectious mass, such as lymphadenitis, instead of a tumor.

Infants and young children may present with fever, malaise, and abdominal, bone, or nonspecific pain, with a



**Figure 5** CT scan revealing a patient with a neuroblastoma.



**Figure 6** An 8-year old with fixed wheezing and a posterior mediastinal mass from a ganglioneuroma.

mass usually noted on abdominal examination but occasionally in the neck or chest. Because of spread to the bone, there may be back or extremity pain, limp, or even paresis. Although a much less common presentation, neuroblastoma may present with symptoms that include failure to gain weight or chronic diarrhea. A syndrome of opsoclonus, dancing eyes, and dancing distal extremity movements will be present less than 5% of the time. Facial signs can include bilateral soft tissue swelling of the eyes, appearing similar to raccoon eyes, secondary to tumor invasion of the bony orbit. Thoracic ganglioneuromas may present on a routine screening CXR or with focal fixed wheezing (Figure 6).

The physical examination requires careful measurement of serial blood pressures to assess for hypertension; a thorough assessment for focal findings in the abdomen, chest, and skin; and a complete neurological examination. Laboratory testing should include CBC, liver function testing, and electrolytes, and urinary catecholamines. Urine should be obtained to test for the catecholamines, vanillylmandelic acid, or homovanillic acid, which are strongly positive in 75% to 90% of children with neuroblastoma [11,13]. Other diagnostic testing should include an abdominal CT, chest radiograph or CT, and skeletal survey to delineate the anatomy and extent of the tumor and to stage the disease [14]. Other testing should be based on clinical findings and may include bone scan to evaluate for bony metastasis. In the differential diagnosis are Wilms tumor, other solid organ cancers, acute leukemia, and infectious diseases, particularly when there is bone disease in the absence of a primary tumor or if the homovanillic acid and vanillylmandelic acid are negative. Transfer to a pediatric referral center is also critical for a timely and accurate diagnosis and to maximize the outcome.

Outcome from neuroblastoma is variable with an overall 85% response to initial therapy and a 50% cure rate [10,13]. Staging (stages 1-4 and 4S) helps to establish a prognosis. Except for 4S, higher stages are associated with both more disseminated disease and poorer outcome. Stage 4S is a phenotype in patients younger than

1 year with localized tumor with dissemination to skin, liver, or bone marrow. This group has less than 10% marrow involvement and much different tumor markers and, overall, does quite well. In most cases, treatment of neuroblastoma includes early surgery, although chemotherapy for the debulking of a large tumor burden is an important consideration. This may also serve to reduce the complication rate of surgery, which has been as high as 25%. In addition to surgery, radiotherapy, and chemotherapy, as well as bone marrow transplant, are all important adjuncts to the treatment of neuroblastoma. In patients with localized disease, surgery alone may be indicated with some adding chemotherapy for tumors that have a genetic marker associated with a poorer prognosis, specifically *MYCN* oncogene amplification. Patients with high-risk disease require aggressive therapy and may have the best prognosis with myeloablative therapy and stem cell or autologous bone marrow transplant. For the practicing clinician, this brings in the full gamut of clinical issues to be aware of from recurrence, complications of myelosuppression, and other immediate problems.

## Summary

The child with cancer can manifest in many ways. They may present with the “classic” signs and symptoms that lead you directly to a diagnosis of childhood leukemia or a cancerous tumor. Alternatively, they may “hide” among the ubiquitous signs and symptoms seen on a nearly daily basis with the many common and less threatening diagnoses we commonly entertain. These atypical presentations may lead to a more extensive and time-consuming workup. One of the most important considerations in the diagnosis of uncommon disorders is to remember to extend the differential diagnosis when the duration of a symptom or the combination of examination findings does not fit with what might be typical for more common and benign diseases. As this article suggests, keep these diagnoses on your list for children with worrisome clinical features or when signs and symptoms persist.

## References

1. Smith MA, Gloeckler Ries LA. Childhood cancer: incidence, survival and mortality. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 1-12.
2. Pizzo PA, Lovejoy Jr FH, Smith DH. Prolonged fever in children: review of 100 cases. *Pediatrics* 1975;55:468-73.
3. Bhatia S, Robinson LL. Epidemiology of leukemia in childhood. In: Nathan D, Orkin S, Grusberg D, Look AT, editors. Nathan and Oski's hematology in infancy and childhood. 6th ed. Philadelphia: Saunders; 2003. p. 1081-100.
4. Silverman LB, Sallan SE. Acute lymphoblastic leukemia. In: Nathan D, Orkin S, Grusberg D, Look AT, editors. Nathan and Oski's hematology in infancy and childhood. 6th ed. Philadelphia: Saunders; 2003. p. 1135-66.

5. Gurney JG, Severson RK, Davis S. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. *Cancer* 1995;75:2186-95.
6. Margolin JF, Steuber CP, Poplack DG. Acute lymphoblastic leukemia. In: Pizzo PA, Poplack DG, editors. *Principles and practice of pediatric oncology*. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 489-544.
7. Grundy PE, Green DM, Coppes MJ, Breslow NE, Ritchey ML, Perlman EJ, et al. Renal tumors. In: Pizzo PA, Poplack DG, editors. *Principles and practice of pediatric oncology*. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 865-92.
8. McHugh K, Pritchard J. Problems in the imaging of three common paediatric solid tumours. *Eur J Radiol* 2001;37:72-8.
9. Blakely ML, Ritchey ML. Controversies in the management of Wilms tumor. *Semin Pediatr Surg* 2001;10:127-31.
10. Merguerian PA, Chang B. Pediatric genitourinary tumors. *Curr Opin Oncol* 2002;14:273-9.
11. Brodeur GM, Maris JM. Neuroblastoma. In: Pizzo PA, Poplack DG, editors. *Principles and practice of pediatric oncology*. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 895-937.
12. Morgenstern BZ, Krivoshik AP, Rodriguez V, Anderson PM. Wilms' tumor and neuroblastoma. *Acta Paediatr Suppl* 2004;445:75-8.
13. Weinstein JL, Katzenstein HM, Cohn SL. Advance in the diagnosis and treatment of neuroblastoma. *Oncologist* 2003;8:278-92.
14. Mehta K, Haller JO, Legasto AC. Imaging neuroblastoma in children. *Crit Rev Comput Tomogr* 2003;44:47-61.