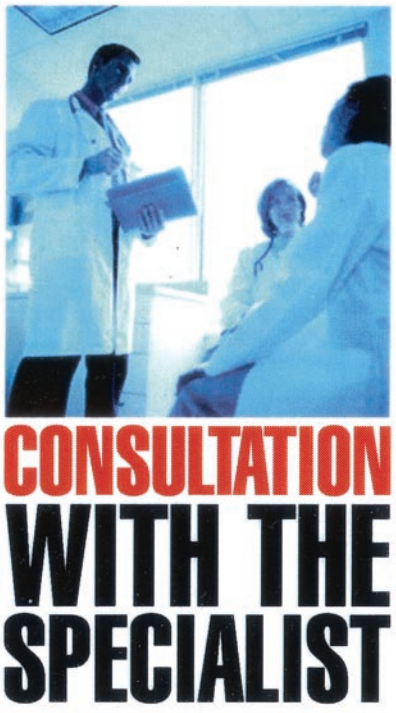

Lymphomas

Maria C. Velez, MD*

Introduction

Lymphomas, which include both Hodgkin and non-Hodgkin, are the third most common childhood malignancy, accounting for approximately 12% of the newly diagnosed cancers seen in children younger than the age of 15 years. Approximately 60% of pediatric lymphomas are non-Hodgkin lymphoma (NHL). Although the incidence of both types of lymphoma increases with age throughout childhood and adolescence, Hodgkin disease (HD) accounts for a greater proportion of the lymphomas seen in adolescents. The crucial role of the pediatrician in the care of the child who has these or other suspected malignancies is maintenance of a high index of suspicion and prompt referral to a pediatric cancer specialist who can initiate the evaluation with dispatch and initiate appropriate diagnosis-directed therapy.

Case Presentation: A Tale of Two Masses

Patient *A* is a 16-year-old African-American male who is brought to the emergency department with a 5-day history of substernal chest pain and shortness of breath. His review of systems is positive for fatigue and cough but negative for fever, weight loss, or night sweats. On physical examination, he is afebrile but tachypneic and tachycardic. He has mild respiratory distress with no retractions, and his lungs are clear to auscultation bilaterally. Heart sounds are distant; peripheral pulses are adequate. There is no significant lymphadenopathy or hepatosplenomegaly.

Patient *B* is an 11-year-old Caucasian male who is brought to his pediatrician for evaluation of shortness of breath and fatigue of 2 to 3 weeks' duration. His mother insists that the child is pale and has less energy than usual. On physical examination, the child is alert and in no distress. His lungs are clear to auscultation bilaterally. There is no significant lymphadenopathy or hepatosplenomegaly.

The initial evaluations for these patients include chest radiography (Figs. 1 and 2).

Clinical Features

HD and NHL have become among the most curable of pediatric malignancies. Today, the projected cure rates for children in certain categories are as high as 90%. For the pediatric oncologist, the index of suspicion of cancer is high, but the opposite is true for most pediatricians and primary care physicians. Although many of the signs and symptoms of HD and NHL are common to both disorders, others are distinctive (Table 1). Some signs and symptoms also are common to other childhood malignancies, and sometimes they are relatively nonspecific, at times mimicking a variety of other more common childhood diseases (Table 2). Constitutional symptoms of fever (>100.4°F [38°C] for 3 consecutive days), night sweats, and unexplained weight loss (10% or more of body weight in the preceding 6 mo) are observed in approximately 25% to 30% of patients who have HD and have a negative impact on the prognosis. These symptoms are related to the production of cytokines by tumor cells. Pruritus also is an occasional presenting symptom. An as-

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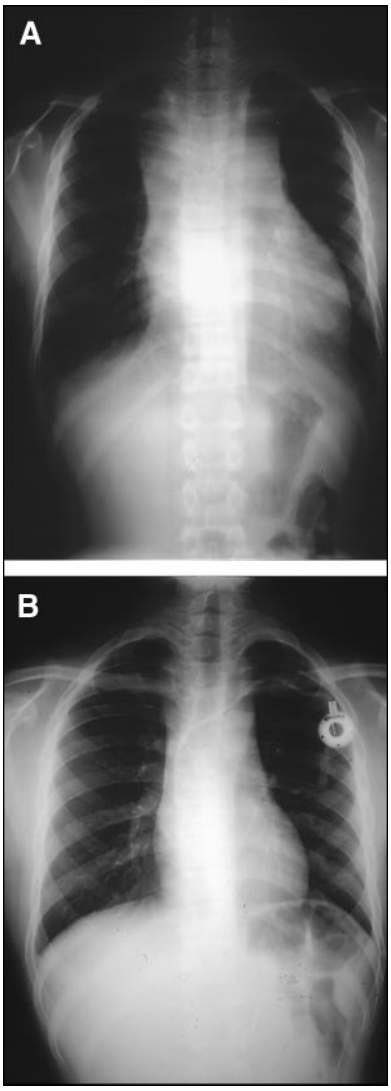

Figure 1. Patient *A* presented with symptoms of respiratory distress of 5 days' duration. Chest radiography revealed a large mediastinal mass with airway obstruction and enlarged cardiac silhouette consistent with pericardial effusion (A). Tissue biopsy confirmed the diagnosis of NHL (T-cell). This case exemplifies the relative short duration of symptoms due to the rapid growth associated with NHL. After 4 weeks of treatment, the patient's chest radiograph demonstrated marked decrease in the size of the mass (B).

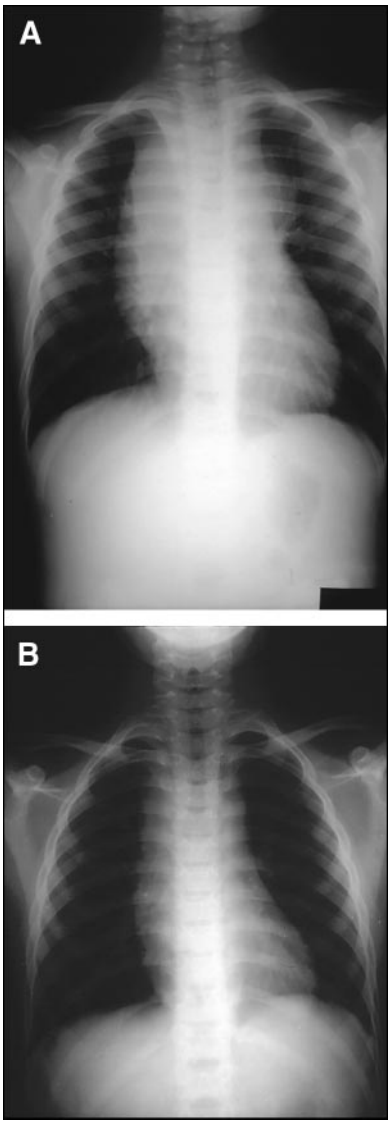

Figure 2. Patient *B* presented with shortness of breath and a complaint of tiredness for 2 to 3 weeks prior to diagnosis. The chest radiograph revealed a large mediastinal mass with deviation of the trachea (A). Tissue biopsy was consistent with HD. Although this patient also presented with respiratory complaints, the onset of clinical symptoms was indolent, which is more consistent with HD. After 4 weeks of treatment, chest radiography demonstrated a very good response, although widening of the mediastinum was observed (B).

sociation with immune-mediated thrombocytopenia purpura has been described in HD, but it is infrequent and does not influence outcome. Weight loss may be seen in children who have NHL. Due to the rapid growth of NHL, symptoms and signs associated with this cancer often have a rapid onset and short duration. The clinical presentation of patient *A* is an example of this. Almost two thirds of children who have NHL have widespread disease at the time of diagnosis that may involve bone marrow, central nervous system (CNS), or both.

The most common initial clinical manifestation of lymphoma is painless lymphadenopathy. Although most children have palpable, small cervical, axillary (<10 mm in greatest diameter), and inguinal (<15 mm in greatest diameter) nodes, considered reactive nodes, adenopathy in the posterior auricular or supraclavicular area is abnormal and deserves further attention. Nodes that are painless, rubbery, firm, and either discrete or matted together characterize lymphomatous involvement, especially in HD. Enlarged nodes associated with any abnormal chest film findings suggest the need for lymph node biopsy, but even in the absence of abnormal chest film findings, biopsy should be performed when lymph nodes as described previously are present. In fact, mediastinal adenopathy can be found in two thirds of the patients, who may present with symptoms of airway obstruction or superior vena cava syndrome. The onset of lymphadenopathy typically is subacute and prolonged for HD and rapid (over the course of few days or weeks) for NHL.

Anterior mediastinal tumors may be asymptomatic or may present with symptoms due to compression of adjacent organs: dysphagia, dyspnea, and pain or swelling of the face, neck,

Table 1. Clinical Presentation of Hodgkin Disease and Non-Hodgkin Lymphoma

Signs and Symptoms	Hodgkin Disease	Non-Hodgkin Lymphoma
Most common sites (lymph node chains)	Cervical, mediastinal, supraclavicular	Abdominal, mediastinal, supraclavicular
Onset of symptoms	Indolent	Rapid
Painless adenopathy	Common	Common
Constitutional symptoms: fever, night sweats, weight loss	Common	Rare
Abdominal symptoms: intussusception, obstruction, abdominal mass	Rare	Common
Symptomatic airway compression	Rare	Common
Superior vena cava syndrome	Rare	Common
Epstein-Barr virus infection	May play a role	Strongly implicated in African Burkitt lymphoma
Incidence of lymphoma in congenital or acquired immunodeficiency	Less common	More common

and upper extremities as a result of superior vena cava syndrome. Subdiaphragmatic disease presenting as the primary disease in HD is rare (<5% of cases). However, in NHL, children who have abdominal masses often present with right lower quadrant tenderness as a result of ileocecal involvement, intestinal obstruction, or intussusception. Lymphoma is the lead point for intussusception in up to 50% of children older than 6 years, and the diagnosis must be strongly considered in any patient older than 3 years who has intussusception. Histologic confirmation always is necessary.

Epstein-Barr virus (EBV), first strongly implicated epidemiologically in African Burkitt lymphoma, appears also to have a role in the pathogenesis of B-cell lymphomas. EBV DNA has been detected in Reed-Stenberg cells (HD), which has led to the speculation that EBV, alone or with other carcinogens, may play a role in the pathogenesis of some cases of HD.

Immunodeficiency disorders (primary, congenital; iatrogenic; acquired; and autoimmune) are associated with an increased incidence of lymphoma, which varies according to the underlying defect. NHL is seen more commonly in patients who have Wiskott-Aldrich syndrome, severe combined immunodeficiency and common variable immunodeficiency syndrome, X-linked lymphoproliferative syndrome, Bloom syndrome, and ataxia-telangiectasia. HD, although diagnosed less commonly, also is seen in these disorders. Posttransplant patients (solid organs and stem cell recipients) also have been identified as being at risk for lymphoid malignancies. The relative risk of developing NHL has been estimated to be 200 to 300 times higher in those infected with human immunodeficiency virus (HIV).

Histopathology

The histopathologic hallmark of HD is the Reed-Sternberg cell, a large cell that has abundant cytoplasm and either multiple or multilobulated nuclei. The four histologic subtypes of HD include:

- Nodular sclerosing, the most common subtype, affecting about 40% of younger patients and 70% of adolescents
- Mixed cellularity, observed in 30% of patients and more commonly in children 10 years of age or younger and in those who have HIV infection
- Lymphocyte predominance, affecting 10% to 15% of children, usually being more common in males and presenting as localized disease
- Lymphocyte-depleted, rarely observed in children (<5%)

In contrast to adult lymphomas, pediatric NHLs show diffuse de-

Table 2. Common, Nonspecific Signs and Symptoms Observed in Childhood Diseases Leading to the Diagnosis of Lymphoma

1. Generalized malaise, fever, adenopathy
2. Headache, nausea, vomiting, weight loss
3. Abdominal pain, intussusception, intermittent obstruction, diarrhea
4. Swelling of face and neck
5. Cough, shortness of breath without fever or history of reactive airways disease, new-onset reactive airways disease

Table 3. Recommended Diagnostic Evaluation for Children Who Have Lymphoma

- Complete history and physical examination
- Complete blood count with differential count, erythrocyte sedimentation rate[1]
- Chemistries: renal and hepatic function tests, serum electrolytes, and mineral panel
- Serum lactate dehydrogenase and uric acid[2]; alkaline phosphatase[3]
- Imaging studies: Chest radiograph, computed tomography (CT) of neck and chest, CT or magnetic resonance imaging of abdomen and pelvis, gallium scan, bone scan[4], lymphangiogram[5]
- Bone marrow examination
- Cerebrospinal fluid examination (cytology)[6]

[1&3]Recommended primarily for Hodgkin lymphoma
[2&6]Recommended primarily for non-Hodgkin lymphoma
[4]If gallium scan suggests bone involvement or for children who have bone pain and elevated alkaline phosphatase level
[5]Only in center that has expertise, not performed routinely

struction of the lymph node architecture. They are all high-grade malignancies. NHLs are apportioned primarily into three major categories: small, noncleaved cell lymphoma (SNCL) (Burkitt and non-Burkitt subtypes) found in about 50% of cases; lymphoblastic lymphoma in about 35% of cases; and large cell NHL in about 15% of cases.

SNCLs express surface immunoglobulins (Igs), almost exclusively IgM, which identify them as B-cell malignancies. They also express B-cell-specific antigens: CD19, CD20, and the common acute lymphoblastic leukemia antigen CD10. These lymphomas generally carry a characteristic chromosomal translocation, invariably involving chromosome 8 at band q24 (the location of the c-myc oncogene known to be a critical gene in the regulation of cell proliferation). The translocation {8; 14} occurs in approximately 80% of the tumors. Less common translocations include {2;8} and {8;22}.

In lymphoblastic lymphomas, the associated chromosomal translocation involves the T-cell receptor genes, particularly T-alpha and -delta situated on chromosome 14q11, especially t{11;14).

Diagnosis and Staging

A careful history and physical examination, paying close attention to all nodal areas, are essential in both types of lymphoma. Because specialized care and resources are required for these patients, referral to a pediatric cancer center is strongly encouraged. Chest radiography (posteroanterior and lateral) provides preliminary information about mediastinal involvement. Lymph node or tissue biopsy is mandatory for histologic diagnosis. Diagnostic imaging studies (computed tomography [CT] and magnetic resonance imaging) provide further information about regional nodal areas as well as pulmonary parenchyma. Infradiaphragmatic diagnostic imaging has become more important because of the infrequent use of surgical staging in children who have HD and are treated with combined modality regimens. Table 3 shows the diagnostic evaluation for children who have HD. The Ann Arbor Staging Classification for HD is shown in Table 4. Such a classification system allows the precise staging that is required for the design and planning of the patient's treatment. The role of surgical staging laparotomy seems to be decreasing with the use of multimodal, aggressive chemotherapy and should be considered only if the find-

Table 4. Ann Arbor Staging Classification for Hodgkin Disease

Stage	Definition
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (III_S) or by localized involvement of an extralymphatic organ or site (III_E) or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement

The absence or presence of fever higher than 100.4°F (38°C) for 3 consecutive days, drenching night sweats, or unexplained loss of 10% or more of body weight in the 6 months preceding diagnosis are to be denoted in all cases by the suffix letters A (asymptomatic) or B, respectively.

ings will alter the recommended therapy significantly.

Due to the very rapid growth rate of NHLs, effective tissue diagnosis and staging is a medical emergency. Tissue biopsy for histologic diagnosis is supplemented wherever possible with immunophenotyping, chromosomal analysis, or molecular studies. The airway should be evaluated by chest radiograph as well as CT of the chest if a mediastinal or paratracheal mass is suspected prior to any diagnostic procedure. Close collaboration with an experienced team of pediatric surgeons and anesthesiologists is mandatory for adequate management of affected patients. Diagnosis should be obtained by the least invasive method possible. The use of general anesthesia or sedation should be avoided to prevent further complications, including death due to tracheal compression. Relevant laboratory investigation should include a complete blood count and chemistries (renal panel, mineral panel, and lactate dehydrogenase) to evaluate for features of acute tumor lysis syndrome (TLS). Appropriate prophylaxis and specific supportive therapy need to be initiated as soon as the diagnosis of NHL is suspected to prevent and treat the potential complications of TLS (Table 5). The most widely used staging system is the St. Jude or Murphy Staging System for NHL (Table 6).

Table 5. Prevention and Treatment of Potential Complications of Tumor Lysis Syndrome

Hydration and alkalinization
$D_5{}^1/_4NS$ with 40 to 80 mEq/L $NaHCO_3$ without potassium at 2 to 4 times maintenance fluid rate. Maintain urine pH at 7.0 to 7.5. Adjust $NaHCO_3$ as needed.
Uric acid reduction
Allopurinol at 300 mg/m^2 per day or 10 mg/kg per day PO or IV or Urate oxidase (rasburicase) IV (0.5 to 0.2 mg/kg per day for 5 d) if indicated
Diuresis
Maintain urine output (>100 mL/m^2 per hour) Furosemide (0.5 to 1.0 mg/kg)
Metabolic/electrolyte abnormalities
Monitor electrolytes, Ca^{+2}, Mg^{+2}, PO_4, and uric acid every 4 to 8 h
Hyperkalemia
Sodium polystyrene sulfonate 1 g/kg Insulin (0.1 U/kg) plus 25% glucose (2 mL/kg) Calcium gluconate (100 to 200 mg/kg)
Hyperphosphatemia
Aluminum hydroxide (15 mL q 4 to 8 h)
Hypocalcemia
Calcium gluconate IV only if symptomatic
Dialysis
Renal failure (anuria, elevated creatinine) Hyperkalemia (potassium >6 mEq/L) Hyperphosphatemia (phosphate >10 mg/dL) Hyperuricemia (uric acid >10 mg/dL) Symptomatic hypocalcemia Volume overload

Treatment and Prognosis

The management of children who have HD requires a multidisciplinary approach led by a pediatric oncologist. The therapy should take into consideration the age and physical maturity of the patient, with the aim of minimizing long-term toxicity without affecting disease-free survival. Most pediatric protocols include multiagent chemotherapy alone or in combination with low-dose, involved-field radiation therapy. This approach decreases both the radiation dose and the chemotherapy exposure, thereby reducing potential long-term sequelae. Combination chemotherapy includes nitrogen mustard/cyclophosphamide, Oncovin® (vincristine), procarbazine, and prednisone (MOPP/COPP); Adriamycin® (doxorubicin), bleomycin, vinblastine, and dacarbazine/etoposide (ABVD/ABVE/ABV); or combinations of these noncross-resistant regimens. Patients who have localized disease (stages I and II) have a greater than 90% survival rate. Children who have advanced stage (stages III and IV) and unfavorable disease (B symptoms of fever and weight loss) and are treated with combination modalities have experienced disease-free survival (DFS) rates of 70% to 90%. The salvage rate in patients who relapse after the initial therapy is significant. If radiation therapy alone is given initially, about 50% to 80% of the patients respond to systemic chemo-

Table 6. St. Jude/Murphy Staging System for Non-Hodgkin Lymphoma

Stage I

- A single tumor (extranodal) or involvement of a single anatomic area (nodal), with the exclusion of the mediastinum and abdomen

Stage II

- Single tumor (extranodal) with regional node involvement
- Two or more nodal areas on the same side of the diaphragm
- Two single (extranodal) tumors, with or without regional node involvement on the same side of the diaphragm
- A primary gastrointestinal tumor (usually ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable

Stage III

- Two single tumors (extranodal) on opposite sides of the diaphragm
- Two or more nodal areas above and below the diaphragm
- Any primary intrathoracic tumor (mediastinal, pleural, thymic)
- Extensive primary intra-abdominal disease
- Any paraspinal or epidural tumor, whether or not other sites are involved

Stage IV

- Any of the above findings with initial involvement of the central nervous system, bone marrow, or both

From Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol.* 1980;7:332–339 with permission.

therapy. If chemotherapy alone is given, salvage with conventional chemotherapy (for patients who experienced initial remissions for 12 months or longer) ranges from 40% to 50% at 5 years. Data on hematopoietic stem cell transplantation after myeloablative chemotherapy suggest progression-free survival rates as high as 50% to 80%. However, as many as 25% of patients may experience transplant-associated mortality due to infectious or cardiopulmonary complications.

Long-term treatment-related complications include cardiopulmonary injury related to doxorubicin and bleomycin, soft-tissue and bone growth alterations after standard and high-dose radiation, and second malignancies. The first two are less common with the use of combined therapy involving low-dose, involved-field radiation and reduced cumulative doses of doxorubicin and bleomycin. The risk of serious bacterial infection, once associated with splenectomy poststaging laparotomy, is seen less frequently now that surgical staging seldom is performed. However, patients who have undergone prior splenectomy or splenic irradiation should receive prophylactic antibiotics and instructions or guidelines to follow during febrile illnesses. Also, patients should be advised about vaccinations against pneumococci, *Haemophilus influenzae*, and meningococci.

The dramatic improvement in the overall survival rate in pediatric NHL can be attributed to the development of highly effective, multiagent chemotherapy regimens under the sponsorship of pediatric oncology cooperative group clinical trials. The chemotherapeutic regimens and duration of therapy vary according to the stage, histology, and immunophenotype of the disease. Due to the rapid growth rate, childhood NHLs respond to a wide range of chemotherapeutic agents, including alkylating agents and antimetabolites such as methotrexate and cytosine arabinoside, among others. Current therapeutic protocols for NHL (B-cell) include intensive, repetitive, short-duration systemic chemotherapy. In T-cell lymphoma, the chemotherapy treatment and duration are similar to or based on regimens used for acute lymphoblastic leukemia. In addition to intensive systemic chemotherapy, CNS prophylaxis is an important component of the treatment protocols.

With the advances in supportive care and the incorporation of intense, aggressive chemotherapy regimens, the survival for early stage disease (stage I/II, nonlymphoblastic) is up to 90% and even approaching 70% survival for children who have advanced disease (stage III/IV, lymphoblastic). Continued improvement in long-term survival with simultaneous minimization of long-term adverse effects and complications remains a major goal of the pediatric oncology community.

The Role of the General Pediatrician

The pediatrician plays a crucial role in the early diagnosis of cancer and the prompt initiation of treatment after referral to a pediatric oncologist. The participation of the pediatrician in the subsequent management of the child who has cancer always is welcome in close consultation and collaboration with the patient's primary oncologist. Becoming familiar with potential problems and complications during treatment is critical. Al-

though childhood lymphomas are highly malignant diseases, treatment has become very rewarding in the practice of pediatric oncology. With improved cure rates, increasing attention now is focused on minimizing late complications of the therapy.

ACKNOWLEDGMENTS

The author thanks Drs. Raj Warrier, Diego Aviles, and especially Dr. Renee V. Gardner for their comments and critical reading of the manuscript.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

11. An 11-year-old boy presents with a 1-week history of right anterior and posterior cervical adenopathy that is painless. The nodes are firm and may be matted together. Complete blood count, electrolytes, uric acid, and calcium and phosphorus levels are normal. The erythrocyte sedimentation rate is 73 mm/h. You refer the child to a surgeon for lymph node biopsy. The *most* important preoperative study(ies) to obtain is (are):

    A. Blood type and cross-match.
    B. Chest radiograph.
    C. Partial thromboplastin time and prothrombin time.
    D. Urinalysis.
    E. Varicella, cytomegalovirus, and measles titers.

12. You and a medical student have just examined a child who has mild bilateral cervical adenopathy likely due to an upper respiratory tract infection. The student asks you which group of lymph nodes most frequently is associated with malignancy when they enlarge. Your *most* likely response is:

    A. Axillary.
    B. Anterior cervical.
    C. Epitrochlear.
    D. Posterior cervical.
    E. Supraclavicular.

13. A 19-year-old boy presents to your office with a temperature of 102°F (38.5°C). He had nodular sclerosing Hodgkin disease diagnosed at 8 years of age. He underwent chemotherapy after a staging laparotomy revealed the disease to be stage III. The next *most* appropriate step you should take at this point is:

    A. Blood culture and administration of intravenous antibiotics.
    B. Chest radiography.
    C. Echocardiography and electrocardiography.
    D. Immediate referral to a pediatric oncologist.
    E. Measurement of serum electrolytes, uric acid, lactic dehydrogenase, calcium, and phosphorus.