#### Lymphoma

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1. A 15-year-old girl presents with 1 month of fatigue and 3 days of chest pain and shortness of breath. Her physical exam is unremarkable. A chest X ray shows a large mediastinal mass that is more than 33% of the diameter of chest cavity. A biopsy shows nodular sclerosing, classic Hodgkin lymphoma (cHL). Metastatic workup at diagnosis including CT scan of the neck, chest, abdomen, and pelvis and PET scan shows no other site of disease.

According to the Ann Arbor staging system, the patient has which stage of cHL?

A. Stage I

B. Stage II

C. Stage III

D. Stage IV

Explanation

The Ann Arbor staging system takes into account that Hodgkin lymphoma typically spreads along contiguous lymph nodes, and extranodal involvement usually results from direct extension of nodal disease. Hematogenous spread does not usually occur until disease is very advanced.

The Ann Arbor staging system:

* Stage I: A single node region (I) or single extranodal organ or site (IE)
* Stage II: Two or more node regions on the same side of the diaphragm (II) or one node region and localized extranodal site on the same side of the diaphragm (IIE)
* Stage III: Node regions involved on both sides of the diaphragm (III) or with localized extranodal site involved (IIIE) or spleen involvement (IIIS)
* Stage IV: Diffuse or disseminated involvement of more than one extranodal site

Extranodal structures contiguous with sites of lymph node involvement are considered E-lesions and include lung, pleural, pericardial, or chest wall infiltration by an adjacent nodal lesion. Pleural and pericardial effusions alone are not considered E-lesions. Liver and bone marrow are not E lesions but are considered stage IV.

Substage classifications are based on defined clinical features and are used in risk stratification. Substage A indicates asymptomatic disease. Substage B indicates the presence of B symptoms, which include fever greater than 38 °C for 3 consecutive days, drenching night sweats, and unexplained weight loss of at least 10% body weight over a 6-month period.

Bulk disease is not part of the Ann Arbor classification but has been used by some groups in risk stratification. Bulk disease includes large mediastinal mass with tumor diameter more than one-third the thoracic diameter on an upright posteroanterior chest X ray, large extramediastinal nodal aggregate measuring more than 6 cm in the longest transverse diameter, and macroscopic splenic nodules seen on CT, PET, or MRI imaging.

2. A 15-year-old girl presents with a 1-month history of fatigue and a 3-day history of chest pain and shortness of breath. Her chest X ray shows a large mediastinal mass that is more than 33% of the thoracic diameter at the level of the diaphragm. A biopsy shows diffuse large B-cell lymphoma. Metastatic workup, including a CT scan of neck, chest, abdomen, and pelvis; bone marrow biopsy; lumbar puncture; and PET scan, shows no other site of disease.

According to the St. Jude (Murphy) staging system, what is the stage of this patient’s non-Hodgkin lymphoma (NHL)?

A. Stage I

B. Stage II

C. Stage III

D. Stage IV

Explanation

The St. Jude (Murphy) staging system frequently is used for NHL in children because the Ann Arbor staging system does not adequately reflect prognosis. Childhood NHL does not progress in the orderly and predictable lymphatic pattern that Hodgkin lymphoma does, and extensive extranodal disease is common.

The St. Jude (Murphy) Staging System for NHL is as follows:

* Stage I: Single nodal or extranodal tumor excluding the mediastinum and abdomen.
* Stage II
	+ Single tumor (extranodal) with regional node involvement, or
	+ Two or more nodal areas on the same side of the diaphragm, or
	+ Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm, or
	+ Primary gastrointestinal tract tumor that is resectable, usually in the ileocecal area with or without involvement of associated mesenteric nodes
* Stage III
	+ Two single tumors (extranodal) on opposite sides of the diaphragm, or
	+ Two or more nodal areas above and below the diaphragm, or
	+ Any intrathoracic disease (lung, pleura, mediastinum, and thymic) or
	+ All extensive, primary intraabdominal disease, or
	+ All paraspinal or epidural disease regardless of other tumor sites
* Stage IV: Bone marrow or central nervous system involvement.

Patients with NHL can present with B symptoms, and these symptoms are more common in anaplastic large-cell lymphoma than in other NHLs. However, unlike in Hodgkin lymphoma, the presence of B symptoms is not used for risk stratification.

3. A 19-year-old college student presents with “lumps” on the right side of his neck and in the right axilla. He had a fever to 39 °C one day in the past week. He has had an unintentional weight loss of 20 pounds over the past 5 months. Physical exam reveals firm anterior cervical and axillary nodes, all more than 2 cm in diameter. A chest X ray shows a large mediastinal mass. A biopsy of the axillary node reveals classic Hodgkin lymphoma.

Which of the following symptoms revealed during the history is a B symptom?

A. Fever to 39 °C

B. 10% weight loss in past 6 months

C. Fatigue

D. Alcohol-induced pain

E. Pruritus

Explanation

The correct answer is B, 10% weight loss in the past 6 months [[AU: BELOW, IT DESCRIBES GREATER THAN 10% WEIGHT LOSS. SHOULD ANSWER OPTION AND THIS EXPLANATION BE CHANGED TO “GREATER THAN 10% WEIGHT LOSS”?]]. In Hodgkin lymphoma, substage classifications are based on defined clinical features and are used in risk stratification. B symptoms include fever greater than 38 °C for at least 3 consecutive days (so option B is incorrect), unexplained weight loss of greater than 10% of body weight over the preceding 6 months, and drenching night sweats (usually necessitating a change of clothing or bedding).

Systemic symptoms are common in patients with Hodgkin lymphoma; however, many of these symptoms, such as anorexia and fatigue, are not B symptoms, so option C is incorrect. Alcohol-induced pain of involved nodal areas (option D) can occur within minutes after alcohol consumption and resolves with treatment of Hodgkin lymphoma. In addition, pruritus (option E) is common at diagnosis, can be mild or severe, and resolves with treatment. The mechanisms of alcohol-induced pain and pruritus are not known.

4. A 12-year-old boy with Wiskott-Aldrich syndrome presents with 3 days of progressive ataxia and slurred speech. An MRI of the brain shows multiple hypodense lesions throughout the cerebrum.

Which of the following conditions is most likely to be revealed from a needle biopsy of one of these brain lesions?

A. Lymphoblastic lymphoma

B. Bacterial abscess

C. Epstein-Barr virus (EBV)+ diffuse large B-cell lymphoma

D. EBV+ Burkitt lymphoma

E. Glioblastoma multiforme

Explanation

Primary CNS lymphoma is extremely rare in pediatric patients, so a workup for immunodeficiency and HIV infection should be considered for any child diagnosed with primary CNS lymphoma. The risk of any lymphoma is greatly increased in any patient with T-cell compromise (HIV infection, transplantation, and inherited T-cell immunodeficiencies). Most lymphomas in immunodeficient patients are B-cell non-Hodgkin lymphoma and often are associated with EBV. Diffuse large B-cell lymphoma is the most common histologic subtype.

5. An 11-year-old boy has been diagnosed with stage IIIB Hodgkin lymphoma with involvement of the mediastinum and para-aortic, iliac, and inguinal nodes. Your treatment plan includes cycles of multiagent chemotherapy and involved-node radiation. The parents are concerned about infertility because their son is too young for sperm donation before therapy.

Which part of therapy would be most likely to cause infertility in this patient?

A. Alkylating agents

B. Radiation

C. Bleomycin

D. Corticosteroids

E. Anthracycline

Explanation

Because the testes are out of the direct field of pelvic radiation, permanent azoospermia is rarely associated with radiation therapy for Hodgkin lymphoma. However, alkylating agents, such as nitrogen mustard, cyclophosphamide, ifosfamide, and procarbazine, are very gonadotoxic to male patients and can result in azoospermia and infertility, depending on the dose. In contrast, female infertility is more strongly associated with radiation (although oophoropexy can be performed to spare some of the radiation effect). Compared with female fertility, male fertility is much more sensitive to alkylating agents, and therefore gender-based therapies have been developed for Hodgkin lymphoma. An example of this is the substitution of etoposide for procarbazine for male patients.

Alkylating agents and topoisomerase II inhibitors have been associated with secondary leukemias and myelodysplasia. Radiation has been associated with thyroid, skin, and breast cancer (particularly in adolescent girls treated for Hodgkin lymphoma). Radiation used to treat Hodgkin lymphoma also has been associated with hypothyroidism, cardiovascular disease (including myocardial infarction and stroke), and spinal growth abnormalities. Bleomycin has been associated with pulmonary fibrosis. Corticosteroids have been associated with cataracts and osteopenia. Anthracyclines are associated with cardiomyopathy.

6. A 12-year-old boy presents with 4 months of painless swelling in his groin and neck. During the past 6 weeks he has had fevers, fatigue, and a 5-lb weight loss. He has been treated with 2 weeks of clindamycin, but lymphadenopathy has not resolved. Physical examination reveals painless inguinal, femoral, cervical, and axillary lymphadenopathy. Lymph nodes are firm, nontender, and nonmobile. A needle biopsy is performed and reveals a hematolymphoid neoplasm that expresses CD30 and evidence of T-cell receptor rearrangement.

What will additional studies most likely reveal?

A. t(2;5)(p23;q35) chromosomal translocation resulting in the nucleophosmin (NPM)-ALK fusion gene

B. t(8;14)(q24;q32) chromosomal translocation involving the cMYC oncogene and the immunoglobulin heavy chain locus

C. Expression of high levels of BCL-6

D. Reed-Sternberg cells

Explanation

This patient has an anaplastic large-cell lymphoma (ALCL), a mature T-cell lymphoma. The majority of ALCLs are characterized by the t(2;5)(p23;q35) chromosomal translocation and NPM-ALK fusion gene. The NPM gene promoter results in overexpression of the ALK kinase in lymphoid cells. Hodgkin lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma (DLBCL) are all mature B-cell lymphomas. Burkitt lymphoma cells contain a translocation involving the cMYC oncogene and one of the following: the immunoglobulin heavy chain locus t(8;14)(q24;q32), the kappa immunoglobulin light chain gene locus t(2;8)(p11;q24), or the lambda immunoglobulin light chain gene locus t(8;22)(q24;q11). Although approximately one-third of pediatric DLBCLs have translocations associated with cMYC, DLBCL has no specific, diagnostic cytogenetic abnormalities. Most cases have complex karyotypes with three or more cytogenetic aberrations. Pediatric DLBCL can express high levels of BCL-6 and CD10. Although some DLBCLs express CD30, they do not express T-cell markers. Reed-Sternberg cells are the malignant cell of Hodgkin lymphoma. Although Reed-Sternberg cells can express CD30, they do not express T-cell markers.

7. A 7-year-old presents with fatigue and abdominal pain. Physical exam reveals a pale child with a distended abdomen. CT scan shows a large abdominal mass encasing bowel and lesions in the kidneys, adrenals, and pancreas. Chemistries reveal elevated LDH, uric acid, and creatinine.

Which of the following is the most likely explanation for the child’s laboratory test results?

A. Sepsis

B. Tumor lysis syndrome

C. Cytokine release from tumor cells

D. Hypovolemic shock

Explanation

Tumor lysis syndrome occurs when renal function cannot sufficiently eliminate the byproducts of rapid tumor cell death. Laboratory abnormalities include hyperuricemia, hyperkalemia, hyperphosphatemia, and associated hypocalcemia. Clinically, hyperuricemia and hyperphosphatemia can result in formation of crystals in the renal tubules and result in renal failure. Hyperkalemia can result in fatal arrhythmias, and hypocalcemia can cause muscle cramps, tetany, laryngospasm, prolonged QTc, and torsade de pointes. Tumor lysis syndrome usually occurs 24 to 72 hours after initiation of therapy. However, bulky, rapidly growing tumors such as Burkitt lymphoma or LL[[AU: LYMPHOBLASTIC LYMPHOMA?]] can present with spontaneous tumor lysis. This is a medical emergency, and management includes frequent monitoring, aggressive hydration, careful electrolyte management, and uric acid reduction by xanthine oxidase inhibition or administration of recombinant urate oxidase.

8. A 3-year-old girl who received a kidney transplant 4 months ago presents with fever. Blood cultures are negative, and fevers persist despite antibiotics. A CT scan is performed to look for a source of infection and reveals a large mass in the liver and enlarged retroperitoneal lymph nodes. A biopsy reveals Epstein-Barr virus (EBV)-positive monomorphic posttransplant lymphoproliferative disease (PTLD).

What is the most appropriate initial treatment at this point?

A. Immunotherapy with a monoclonal antibody against CD20

B. Ganciclovir and intravenous immunoglobulin

C. B-cell non-Hodgkin lymphoma therapy for stage III disease

D. Reduction of immunosuppression

E. Low-dose chemotherapy such as cyclophosphamide and prednisone

Explanation

PTLD occurs in 5% to 10% of children undergoing organ transplantation. The majority (more than 70%) is associated with EBV and B-cell disease. PTLD often is extranodal, and the allograft is a common site of disease. Monomorphic PTLD often resembles DLBCL and, less often, Burkitt lymphoma or even Hodgkin lymphoma. The disease can be polyclonal or monoclonal. Reduction of immunosuppression usually is the first intervention and can result in complete regression of disease. There is no evidence that antiviral therapies by themselves are effective in treating PTLD. For patients who do not respond to reduction of immunosuppression, low-dose chemotherapy or immunotherapy can achieve durable remission for about two-thirds of patients.

9. An 8-year-old boy presents with a 2-week history of history of intermittent abdominal pain, vomiting, and gastrointestinal bleeding. Physical examination findings are consistent with an acute abdomen. CT demonstrates an ileocecal mass and intussusception.

What is the most likely diagnosis?

A. Anaplastic large-cell lymphoma

B. Diffuse large-cell lymphoma

C. Burkitt lymphoma

D. Lymphoblastic lymphoma

E. Hodgkin lymphoma

Explanation

Lymphomas involving the ileocecal region in children are almost always Burkitt (or Burkitt-like). Sporadic Burkitt lymphoma commonly presents as an abdominal mass in boys aged 5 to 10 years. Clinically, they can present with abdominal pain, distension, emesis, gastrointestinal bleeding, or (rarely) perforation. An ileocecal intussusception is present in up to 30% of patients, and the resulting pain or mass in the right lower quadrant can be confused with acute appendicitis. Of note, because intussusception can result in early detection of cancer, these patients can often be cured with minimal chemotherapy.

10. An 8-year-old boy presented with severe abdominal pain, vomiting, gastrointestinal bleeding, and fever. Abdominal ultrasound suggested appendicitis. The patient was taken to surgery, and an enlarged appendix was removed. The pathology review of the appendix revealed a single focus of Burkitt lymphoma. Metastatic workup including CSF; bone marrow; CT scan of the neck, chest, abdomen, and pelvis; and PET scan revealed no other sites of disease.

According to the St. Jude (Murphy) staging system, what is the most appropriate stage for this patient?

A. Stage I

B. Stage II

C. Stage III

D. Stage IV

Explanation

A primary gastrointestinal tract non-Hodgkin lymphoma that is resectable is stage II, according to the St. Jude (Murphy) staging system, whereas all extensive, primary intraabdominal disease is stage III. Unfortunately, the majority of patients with abdominal Burkitt lymphoma have large tumor burden that can involve the mesentery, retroperitoneum, kidneys, ovaries, and peritoneal surfaces and can be associated with malignant ascites. For these patients, surgical debulking is not appropriate.

11. A 12-year-old girl presents with 6 months of red-brown raised skin lesions that become hemorrhagic, crusted, and disappear after 3 to 4 weeks. During the past week, she has had fatigue, fevers, anorexia, and a 10-lb weight loss. Physical exam reveals several raised, red-brown lesions with about 1 cm subcutaneous firmness on the patient’s arms, a 4-cm skin lesion on her abdomen that has a necrotic center, and a 3-cm axillary node. Metastatic workup shows only the enlarged axillary node. The axillary node and all of the skin lesions are PET scan positive.

Which of the following is the most likely diagnosis?

A. Hodgkin disease

B. Burkitt lymphoma

C. Diffuse large B-cell lymphoma (DLBCL)

D. LL[[AU: LYMPHOBLASTIC LYMPHOMA?]]

E. Anaplastic large-cell lymphoma (ALCL)

Explanation

Although a number of lymphomas can involve the skin, ALCL is the most common in children. Early lesions can spontaneously regress and, if biopsied, be very difficult to distinguish from lymphomatoid papulosis. Clinical symptoms in ALCL are quite variable, with B symptoms being more common than in other non-Hodgkin lymphoma. The pathologic diagnosis can be difficult to make. Immunophenotyping can be helpful because all ALCLs will express CD30, differentiating it from DLBCL, but most Hodgkin disease is CD30(+). CD45 is helpful in distinguishing between ALCL, which is CD45(+), and Hodgkin disease, which is CD45(–). Cytogenetics can be very helpful because the t(2;5) translocation resulting in the fusion NPM-ALK protein is diagnostic of ALCL.

12. A 4-year-old boy presents with a 6-week history of swelling below his jaw that has been slowly growing despite a 2-week course of antibiotics. Examination reveals a firm, fixed, nontender, 3-cm lymph node. Biopsy is performed. Histology shows nodular collections of small lymphocytes and histiocytes with scattered mononuclear cells, with convoluted irregular nuclei and occasional small nucleoli. By immunohistochemistry these cells are positive for CD19, CD20, CD79a, CD45, and BCL-6 but are negative for CD15, CD30, and EBV markers. Fluorescence *in situ* hybridization for MYC translocations is negative.

Which of the following is the most likely diagnosis?

A. Classic Hodgkin lymphoma

B. Nodular lymphocyte-predominant Hodgkin lymphoma (nLPHL)

C. Burkitt lymphoma

D. Diffuse large B-cell lymphoma

E. Lymphadenitis from atypical mycobacteria

Explanation

nLPHL is a B-cell lymphoma that is significantly different from Hodgkin lymphoma. nLPHL accounts for 10% to 20% of pediatric Hodgkin lymphoma; usually presents with early stage disease (IA, IIA); and has a male predominance, indolent course, and good prognosis but can have late and occasionally multiple relapses. The malignant cells of nLPHL are lymphocyte-predominant cells (formerly known as lymphocytic and histiocytic variants of Reed-Sternberg cells) and show a phenotype consistent with germinal center B cells. By immunohistochemistry the malignant cells will be positive for CD20, CD45, CD79a, PAX5, and BCL-6 but negative for CD10, CD15, and CD30. They also will express RNA transcription factors octamer-binding transcription factor 2 (Oct-2) and B-cell Oct-binding protein 1 (BOκ light chain, or λ immunoglobulin light B.1). In contrast, classic Hodgkin lymphoma usually shows Reed-Sternberg cells and has an immunophenotype that includes CD15+, CD30+, and stains for EBV antigens in 40% to 50% of cases. Patients with Burkitt lymphoma have translocations t(8;14)(q24;q32) in 70% to 80% of patients and t(2;8)(p12;q24) or t(8;22)(q24;q11) in 10% to 15% of patients. These translocations involve the cMYC oncogene and the immunoglobulin heavy chain, chain gene loci, respectively. Patients with DLBCL also can express BCL-6 and MYC. Both Burkitt and DLBCL are aggressive, mature B-cell lymphomas; express B-cell markers; and are readily detectable by flow cytometric analysis.

13. A 2-year-old boy presents with a 2-week history of painless, left-sided neck swelling that was not responsive to antibiotics. He had no fever; night sweats; weight loss; or other evidence of upper respiratory infection, otitis, or pharyngitis. Complete blood counts and serum chemistries (including uric acid and LDH) were normal. CT imaging showed extensive, bulky lymphadenopathy with mild adjacent inflammatory stranding in the left lateral aspect of the neck, extending into the supraclavicular space and left carotid space. The largest lymph nodes measured 3 cm in diameter and caused mild mass effect on the hypopharynx. Excisional biopsy of a lymph node was performed and showed multiple very large histiocytes with large central ovoid nuclei with prominent central nucleoli in the lymph node sinuses. Within the histiocyte cytoplasm, multiple lymphocytes, neutrophils, and erythrocytes surrounded by a thin clear rim could be seen. Immunostains of the histiocytes were positive for Fascin, CD68, CD163, and S100 but were negative for CD1a.

Which of the following is the most likely diagnosis?

A. Classic Hodgkin lymphoma, mixed cellularity subtype

B. Nodular lymphocyte-predominant Hodgkin lymphoma

C. Langerhans cell histiocytosis

D. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

E. Infectious mononucleosis

F. Anaplastic large-cell lymphoma

Explanation

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is a nonmalignant lymphoproliferative disorder with a typical presentation of fever, leukocytosis, and painless cervical lymphadenopathy. Although it often localizes to the head and neck, extranodal sites are involved in approximately 40% of cases and can include skin, soft tissue, the central nervous system, and, less commonly, the gastrointestinal tract. The hallmark of the disease is emperipolesis, the nondestructive phagocytosis of lymphocytes or erythrocytes. Histocytes will stain positive for CD68 (KP-1), CD163, and S100 but typically are negative for CD1a (unlike Langerhans cell histiocytosis). Other benign lymphoproliferative conditions that can mimic lymphoma include histocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease), progressive transformation of germinal centers, and Castleman disease. Autoimmune diseases also can present with significant lymphadenopathy.

14. A 5-year-old boy presents with 1 week of fevers, weight loss, and swollen abdomen. Complete blood counts are normal, but serum chemistries show hyperkalemia, hyperuricemia, hyperphosphatemia, and LDH of 3,900 IU/L (four times the upper limit of normal). CT shows diffuse mesenteric lymphadenopathy. Biopsy shows malignant cells that express CD10, CD19, CD20, CD22, and surface IgM. Ninety-nine percent of cells are positive for Ki-67+. Cytogenetics reveal a t(8;14) translocation. CNS and bone marrow are negative for malignancy.

For this disease, which of the following factors influence prognosis?

A. LDH

B. Uric acid

C. B symptoms (fevers, night sweats, weight loss)

D. t(8;14) translocation

E. CD20 expression

Explanation

This patient has stage III Burkitt lymphoma, as indicated by diffuse abdominal involvement. Non-Hodgkin lymphomas (NHLs) are staged according to the St. Jude (Murphy) system. High LDH is a negative prognostic feature in Burkitt lymphoma in both Berlin-Frankfurt-Munster and French-American-British Society of Pediatric Oncology trials. Elevated uric acid indicates spontaneous tumor lysis but is not predictive of response to therapy, per se. The Ann Arbor stages of Hodgkin lymphoma are subclassified into “A” or “B” based on the absence or presence of systemic systems. Although B symptoms are prognostic in Hodgkin lymphoma, they are not used for risk stratification of NHL. cMYC is a transcription factor on chromosome 8 that acts like an oncogene and drives proliferation. Common translocations in Burkitt lymphoma are t(8;14)(q24;q32) IgM-cMYC in about 80% of cases, t(2,8)(p11;q24) IgK-cMYC in 15% of cases, and t(8;22)(q24;q11) IgL-cMYC in 5% of cases. Although important for diagnosis, the translocations are not used in risk stratification. Finally, although many Burkitt lymphomas express the surface marker CD20, and immunotherapy using antibodies against CD20 has been shown to improve outcomes in adults with CD20-positive lymphomas such as diffuse large B-cell lymphoma, the presence of CD20 on pediatric Burkitt lymphoma is not a prognostic marker.

15. A 13-year-old girl presents with 2 months of progressive, painless cervical and supraclavicular lymphadenopathy, malaise, intermittent temperatures to 99 °F, 2-lb weight loss, and an intermittent cough. Chest X ray reveals an anterior mediastinal mass that occupies less than one-third of the thoracic diameter. CBC shows mild microcytic anemia, mildly elevated ESR, and normal electrolytes and LDH. Biopsy of the cervical lymph node shows many scattered binuclear cells with a thick nuclear membrane, pale chromatin, large eosinophilic nucleoli, and an inflammatory background containing lymphocytes, eosinophils, plasma cells, and histiocytes. By immunohistochemistry the binucleated cells stain positive for CD15 and CD30 but are negative for CD45. Fluorodeoxyglucose PET shows increased uptake in the cervical nodes and mediastinal mass only. CT shows cervical and supraclavicular lymphadenopathy involving two nodal groups, with the largest nodal aggregate measuring 4 cm in the longest transverse diameter. There are no additional lymphadenopathy, hepatosplenomegaly, splenic nodules, or focal defects.

Which of the following is this patient likely to have?

A. Low-risk classic Hodgkin lymphoma

B. Low-risk classic nodular lymphocyte-predominant Hodgkin lymphoma (nLPHL)

C. Low-risk anaplastic large-cell lymphoma

D. None of the above; bilateral bone marrow biopsies are necessary for staging and risk stratification

Explanation

This patient has stage IIA, nonbulky, mixed cellularity, classic Hodgkin lymphoma and is considered to be at low risk.

The malignant cell of classic Hodgkin lymphoma is the Reed-Sternberg cell. The malignant cell of nLPHL is the lymphocyte-predominant cell, a mononuclear variant of the Hodgkin and Reed-Sternberg cell, which generally has a convoluted irregular nucleus and several small nucleoli (sometimes called “popcorn cells”). Classic Hodgkin lymphomas tend to stain positive for CD15 and CD30 but are negative for CD45, whereas nLPHLs stain positive for CD45 but are negative for CD15 and CD30. Classic Hodgkin lymphoma is more common than nLPHL and anaplastic large-cell lymphoma, the latter of which usually presents with more advanced disease.

Although she has mild constitutional symptoms including malaise, elevated temperatures, and mild weight loss, these do not meet criteria for B symptoms. Because her mediastinal mass is less than one-third of the thoracic diameter, and her largest nonmediastinal nodal aggregative is less than 6 cm in longest transverse diameter, she does not have bulky disease. In the past, splenectomy was used as part of staging for abdominal involvement of Hodgkin lymphoma; however, with advances in imaging modalities, this practice was abandoned long ago. Although the major pediatric cooperative oncology consortia vary in their risk stratification of Hodgkin lymphoma, nonbulky stage IIA is nearly always low risk.

Staging for advanced Hodgkin lymphoma often involves bilateral bone marrow biopsies and aspirates. However, recent data suggest that PET-CT has greater sensitivity and specificity for detecting bone marrow disease than bone marrow biopsies and aspirates. Because this patient has no evidence of marrow disease on PET imaging and has limited stage disease (IIA, nonbulky), it is highly unlikely that a bone marrow biopsy would reveal marrow involvement and up-stage this patient. Thus, many investigators do not perform bilateral bone marrow biopsies in the evaluation of low-stage Hodgkin lymphoma based on clinical presentation and imaging. The ability of PET imaging to completely replace bone marrow analysis for all patients newly diagnosed with Hodgkin lymphoma is under investigation.

16. A 6-year-old boy presents with rapidly increasing abdominal girth, abdominal pain, and bilious emesis. On examination, his abdomen is distended, and he has mild, diffuse tenderness to palpation without rebound or guarding. Laboratory studies reveal pancytopenia and a markedly elevated LDH. Review of the peripheral smear reveals circulating blasts with oval nucleus, small but distinct nucleoli, and a modest amount of deep blue cytoplasm with prominent vacuoles. CT reveals diffuse abdominal lymphadenopathy with tumor involving the mesentery, retroperitoneum, and kidneys. The patient has not yet received chemotherapy or steroids.

Based on your suspected diagnosis, which of the following is an immediate risk for this patient?

A. Tumor lysis syndrome

B. Superior vena cava syndrome

C. Superior mediastinal syndrome

D. Spinal cord compression

E. Intestinal perforation

**Explanation**

Based on presentation, disease location, blast histology, and cytopenias, the patient likely has Burkitt leukemia. The most common site of disease in sporadic cases of Burkitt lymphoma is the abdomen. Patients are most often boys aged 5 to 10 years who present with nausea, vomiting, abdominal pain or distension, and GI bleeding. Intestinal perforation can occur but is rare. Even before the initiation of chemotherapy, patients with high-grade Burkitt leukemia or lymphoma are at high risk of spontaneous tumor lysis syndrome. Risk factors include large tumor burden, elevated LDH, and renal involvement of disease. Although prophylaxis with recombinant xanthine oxidase reduces this risk, it remains greater than 10% of cases. Although Burkitt lymphoma can involve the mediastinum, presentation in this location is very rare.

17. A 12-year-old boy presents with 2 weeks of cough, fatigue, dyspnea, dysphagia, chest pain, low-grade fevers, and an 8-lb weight loss. Imaging reveals a large anterior mediastinal mass, a pericardial effusion, and bilateral pleural effusions. He has a normal CBC, electrolyte panel, and coagulation studies.

What is the most likely diagnosis?

A. Primary mediastinal B-cell lymphoma

B. Anaplastic large-cell lymphoma

C. Nodular sclerosing Hodgkin lymphoma

D. T-cell lymphoblastic lymphoma

Explanation

This is classic presentation for T-cell lymphoblastic lymphoma. Lymphoblastic lymphoma accounts for approximately 20% of pediatric non-Hodgkin lymphoma (NHL). Approximately 75% of lymphoblastic lymphomas are T lineage, and 90% are stage III or IV. They frequently present in the mediastinum, neck, and chest, and symptoms are related to mass effect and malignant effusions. Hodgkin lymphoma tends to present with painless lymphadenopathy, a mediastinal mass with or without constitutional symptoms (B symptoms). Pleural effusions in Hodgkin lymphoma are rare. Anaplastic large-cell lymphoma is often slowly progressive and more often involves skin, lymph nodes, or bone lesions. Primary mediastinal B-cell lymphoma can be associated with both pleural and pericardial effusions, but this entity is much less common and accounts for only 1% to 2% of pediatric NHL.

18. A 17-year-old boy presents with 2 weeks of worsening fatigue, cough, and shortness of breath. He is tachypneic, but oxygen saturation is normal. X ray reveals a large anterior mediastinal mass and a large left-sided pleural effusion. CT imaging shows minor airway compression of the distal trachea and left main stem bronchus and no pericardial effusion.

What is the most appropriate next step in this patient’s care?

A. Intubation for airway protection

B. Thoracentesis

C. Radiation to the mediastinal mass

D. Empiric steroid therapy

E. Incisional biopsy of the mediastinal mass

F. Bone marrow biopsy followed by cytoreductive therapy with steroids

Explanation

Patients with large anterior mediastinal masses are at risk of superior vena cava syndrome and superior mediastinal syndrome. In such circumstances it is important to obtain diagnostic tissue in the least invasive way possible. In this case, although the patient does have a large mediastinal mass, he has only minimal airway compression when recumbent, and so it is most likely that the pleural effusions are the cause of his symptoms. Draining the pleural effusion via thoracentesis likely will alleviate his respiratory symptoms, and the pleural fluid may contain sufficient material for diagnosis. Bone marrow biopsy, although also relatively noninvasive, may or may not yield the diagnosis in the presence of a normal CBC and will not relieve the patient’s symptoms. Intubating a patient with a mediastinal mass is inappropriate because it can be difficult to intubate past an airway obstruction, and the anesthesia can increase compression of the airway or superior vena cava. Thus, incisional biopsy of the mediastinal mass, because it requires greater sedation than a thoracentesis, is incorrect as the first step. Empiric therapy with either steroids or radiation to the mediastinal mass is inappropriate (in this case) because the mass is not causing symptomatic compression of the superior vena cava or airways, and either therapy may make diagnosis more difficult.

19. A 13-year-old girl presented with fevers, fatigue, tachypnea, shortness of breath, and abdominal pain. Imaging revealed abdominal lymphadenopathy, ascites, a pericardiophrenic mass, and pleural effusion. She underwent a therapeutic thoracentesis. Malignant cells were seen in the pleural fluid and were found to express surface IgG, CD19, CD20, CD22, CD30, CD79a, PAX-5, BCL-6, and cMYC.

What is the most likely diagnosis?

A. Classic Hodgkin lymphoma

B. Nodular lymphocyte-predominant Hodgkin lymphoma

C. Anaplastic large-cell lymphoma

D. Burkitt lymphoma

E. Diffuse large B-cell lymphoma (DLBCL)

Explanation

DLBCLs demonstrate a mature B-cell phenotype including expression of surface IgG, CD19, CD20, CD22, CD79a, and PAX-5. Some cases of DLBCL express CD30 as a nonspecific activation marker, which may place classic Hodgkin lymphoma in the differential diagnosis. Although cMYC is expressed in Burkitt lymphoma, it has also been reported in 30% to 40% of DLBCLs. BCL-6 is expressed in 60% to 80% of pediatric DLBCLs but is not seen in Burkitt lymphoma. The presence of a t(14;18) translocation or Ki67 staining of less than 95% would also help rule out Burkitt lymphoma. Classic Hodgkin lymphomas express CD15 and CD30, but B-cell markers are downregulated. Nodular lymphocyte-predominant Hodgkin lymphomas also express B-cell markers CD19, CD20, and CD79a, but they also express CD45 and lack CD15 and CD30. Anaplastic large-cell lymphoma expresses CD30; however, anaplastic large-cell lymphoma is a mature T-cell lymphoma and lacks B-cell markers.

20. A 15-year-old girl presents with stage IIIB nodular sclerosing Hodgkin lymphoma involving thoracic and abdominal lymph nodes. PET imaging shows no other sites of disease. After two cycles of chemotherapy, her lymph nodes have all decreased in size, with the largest nodal aggregate deceasing from 13 cm in its longest axis to 6 cm. Her mediastinal mass has reduced in diameter by half. Her tumor remains PET-avid with maximal standard uptake values in the nodal aggregate of 2.1 compared with 2.8 in the mediastinum.

Which of the following most accurately describes her response to therapy?

A. Complete metabolic response

B. Partial response

C. Stable disease

D. Refractory disease

Explanation

The Deauville score is a 5-point scale used to assess fluorodeoxyglucose (FDG) avidity in both Hodgkin and non-Hodgkin lymphoma. It is internationally accepted as the standard of care for evaluation of response to therapy in Hodgkin lymphoma.

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| --- | --- |
| Deauville Score | FDG-PET Result |
| 1 | No uptake above background |
| 2 | Uptake ≤ mediastinum |
| 3 | Uptake > mediastinum but ≤ liver |
| 4 | Uptake moderately increased compared with the liver at any site |
| 5 | Uptake markedly increased compared with the liver at any site |
| X | New areas of uptake that are considered unlikely to be related to lymphoma |

A Deauville score of 1 to 3 is generally accepted as metabolic complete remission. However, to prevent undertreatment, some clinical trials testing reduction of therapy consider a Deauville score of 3 as an inadequate response. A Deauville score of 1 or 2 is always considered a metabolic complete remission, and when it occurs during an interim analysis, it is usually associated with good prognosis with standard care. In patients with the nodular sclerosing subtype of Hodgkin lymphoma, it is common to have a complete metabolic response despite residual mass.

21. A 15-year-old girl presents with 1 week of fatigue, nausea, headaches, and diffuse myalgias. CBC with automated differential revealed anemia (Hgb 8.9 g/dL), thrombocytopenia (Plt 132,000/µL), a WBC of 49,000, and differential showing 58% neutrophils, 7% band cells, 38% lymphocytes, and 3% monocytes. Imaging shows hematosplenomegaly and prominent cervical, abdominal, and pelvic lymph nodes. There is no mediastinal mass. Testing for Epstein-Barr virus and hemophagocytic lymphohistiocytosis (HLH) was negative. Over the next few days she developed progressive tachypnea, hypoxia, hypotension followed by respiratory failure, and septic shock. Blood cultures and HLH testing were negative. A hematopathologist reviews the peripheral smear and notes a subpopulation of large lymphocytes, mainly by the feathered edge with clumped chromatin, distinct nucleoli, and abundant cytoplasm. Cells stain negative for CD3, CD4, CD8, and TdT but are positive for CD7.

What is the most likely diagnosis?

A. T-lymphoblastic leukemia

B. T-lymphoblastic lymphoma

C. Anaplastic large-cell lymphoma (ALCL)

D. B-lymphoblastic leukemia

E. Diffuse large B-cell lymphoma

Explanation

Bone marrow biopsy confirmed ALK+ small-cell variant ALCL with heterogenous CD30 expression. As in this case, ALCL cells are often negative for surface expression of CD3, although TCR gene rearrangements can be detected. Although categorized as mature T-cell lymphomas, they may not express surface CD4 or CD8. They can have a biomass 25 times that of resting lymphocytes, and they can be found at the feathered edge because of the process of making the peripheral smear. It is not uncommon for an automated differential to miss malignant ALCL cells.

22. A 3-year-old boy presents to your office with a 4 cm × 5 cm raised, erythematous, purplish mass of the scalp on the right side of his face. CBC is normal, and imaging shows no other sites of disease. Biopsy reveals small round blue cells that stain for CD10, CD19, CD22, CD24, CD79a, and nuclear TdT. The diagnosis of B-lymphoblastic lymphoma is made.

Which clinical feature of this patient confers a significantly increased risk of relapse?

A. Age at diagnosis

B. WBC count less than 10,000 at diagnosis

C. Hyperdiploid cytogenetics

D. Extranodal (skin) involvement

Explanation

Unlike in acute lymphoblastic leukemia in which patients are older than 10 years at diagnosis, in B lymphoblastic lymphoma, patients younger than 4 years at diagnosis have a significantly higher risk of relapse (about 45%) compared with children 4 to 15 years of age (about 5%). Currently, WBC count and hyperdiploid cytogenetics are not used for risk stratification. Skin is involved in about 37% of cases of B-lymphoblastic lymphoma and is not prognostic.

23. A 16-year-old girl presents to your office with diffuse supraclavicular, cervical, and axillary lymphadenopathy that has been progressing over the past 2 weeks. Imaging also reveals an anterior mediastinal mass and small pleural effusion. She has no cough, respiratory distress, or airway or tracheal compression. She completed therapy for lymphoma 13 months earlier, and her clinical course was complicated by multiple episodes of severe mucositis, sepsis in the setting of severe neutropenia, and acute kidney injury.

Which diagnosis would allow the greatest likelihood of attaining a sustained second remission with minimal toxicity?

A. B-lymphoblastic lymphoma

B. Diffuse large B-cell lymphoma

C. Burkitt lymphoma

D. T-lymphoblastic lymphoma

E. Anaplastic large-cell lymphoma (ALCL)

Explanation

Patients with relapsed ALCL can often achieve sustained remission with minimal toxicity using monotherapy with vinblastine, ALK inhibitors, or antibody drug conjugate targeting CD30 (brentuximab vedotin). Although sustained remission has been reported, the optimal duration of treatment with such agents and the likelihood of cure with such minimal therapy have yet to be determined. In contrast, relapsed B-cell non-Hodgkin lymphomas (B-lymphoblastic lymphoma, diffuse large B-cell lymphoma) all have very poor prognoses and need multiagent high-dose chemotherapy and stem cell transplantation for cure. T-lymphoblastic leukemia and T-lymphoblastic lymphoma have similarly poor prognoses.