#### Lymphoma

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1. A 15-year-old female 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 greater than 33% of the diameter of her chest cavity. A biopsy shows nodular sclerosing, classic Hodgkin lymphoma (cHL). Metastatic workup at diagnosis, including CT scan of 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

**Question 1**

**Answer:** A

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

A. Stage I: A single node region (I) or single extranodal organ or site (IE)

B. 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)

C. Stage III: Node regions involved on both sides of the diaphragm (III) or with localized extranodal site involved (IIIE) or spleen involvement (IIIS)

D. 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 greater than one-third of the thoracic diameter on an upright posterioranterior chest x-ray, large extramediastinal nodal aggregate measuring greater than 6 cm in the longest transverse diameter, and macroscopic splenic nodules seen on CT, PET, or MRI imaging.

1. A 15-year-old female presents with 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 greater than 33% of the thoracic diameter at the level of the diaphragm. A biopsy shows diffuse large B-cell lymphoma. Metastatic work-up, including a CT scan of neck, chest, abdomen, and pelvis; bone marrow biopsy; lumbar puncture; and PET scan show 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

**Question 2**

**Answer:** C

Explanation

The St. Jude (Murphy) staging system frequently is used for non-Hodgkin lymphoma (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

A. Stage I: Single nodal or extranodal tumor excluding the mediastinum and abdomen

B. Stage II:

a) Single tumor (extranodal) with regional node involvement, or

b) Two or more nodal areas on the same side of the diaphragm, or

c) Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm, or

d) Primary gastrointestinal tract tumor that is resectable, usually in the ileocecal area with or without involvement of associated mesenteric nodes

C. Stage III:

a) Two single tumors (extranodal) on opposite sides of the diaphragm, or

b) Two or more nodal areas above and below the diaphragm, or

c) Any intrathoracic disease (lung, pleura, mediastinum, and thymic) or

d) All extensive, primary intraabdominal disease, or

e) All paraspinal or epidural disease regardless of other tumor sites

D. Stage IV: Bone marrow and/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 other NHL. However, unlike in Hodgkin lymphoma, the presence of B symptoms is not used for risk stratification.

1. A 19-year-old freshman in college presents with “lumps” on the right side of his neck and in the right axilla. He had a fever to 39 °C 1 day in the past week. On physical exam, there are firm anterior cervical and axillary nodes, all greater 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. Pruritis

F. A and B

**Question 3**

**Answer:** B

Explanation

In Hodgkin lymphoma, substage classifications are based on defined clinical features and are used in risk stratification. B symptoms include (a) fever higher than 38 °C for at least 3 consecutive days, (b) greater than 10% unexplained weight loss over the preceding 6 months, and (c) drenching night sweats (usually requiring changing of clothing and/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. Alcohol-induced pain of involved nodal areas can occur within minutes after alcohol consumption and resolves with treatment of Hodgkin lymphoma. In addition, pruritis is common at diagnosis, can be mild or severe, and resolves with treatment. The mechanism of neither alcohol-induced pain nor pruritis is known.

1. A 17-year-old female presents with cervical adenopathy and a history of daily fevers and drenching night sweats. A biopsy is performed and reveals classic Hodgkin lymphoma. Which of the following is least appropriate as part of the staging workup?

A. Chest x-ray

B. CT scan of chest, abdomen, and pelvis

C. Functional imaging (PET scan)

D. Lumbar puncture and cererbrospinal fluid (CSF) analysis

E. All of the above are indicated

**Question 4**

**Answer:** D

Explanation

Central nervous system (CNS) involvement by Hodgkin lymphoma is exceedingly rare. Evaluation of the CNS is not routine practice, and CNS prophylaxis is not part of therapy for Hodgkin lymphoma. In contrast, the common pediatric non-Hodgkin lymphoma (NHL) can be widely disseminated at presentation even when the patients appear to present with localized disease on physical examination. Evaluation of CNS with lumbar puncture and CSF cytology is important in the staging workup for pediatric NHL, and CNS prophylaxis is part of treatment for most pediatric NHL.

1. Which of the following uses of radiation is considered standard practice in pediatric lymphoma?

A. Involved node radiation for anaplastic large-cell lymphoma with residual mass after two cycles of chemotherapy

B. Central nervous system (CNS) radiation for Burkitt lymphoma with CNS disease at diagnosis

C. Prophylactic CNS radiation for all patients with stage III lymphoblastic lymphoma

D. Involved node radiation to PET-avid residual tumor mass (with uptake markedly increased compared with the liver) after chemotherapy for a patient with stage IIIB nodular sclerosing Hodgkin lymphoma

**Question 5**

**Answer:** D

Explanation

The use of low-dose involved field radiation is a routine component of treatment for pediatric patients with high-risk Hodgkin lymphoma who do not obtain a complete metabolic remission following chemotherapy. However, because radiation to the mediastinum of females is associated with a significant increased risk of breast cancer, clinical trials have been designed to test the hypothesis that radiation therapy can be reduced or eliminated for subsets of patients with Hodgkin lymphoma who have complete and rapid response to chemotherapy.

Radiation therapy has not been shown to improve outcomes for most pediatric non-Hodgkin lymphomas (NHL). In pediatric NHL, radiation therapy is reserved for patients with life-threatening emergencies at diagnosis, such as airway compression due to a mediastinal mass. Some patients with lymphoblastic lymphoma with central nervous system (CNS) disease at diagnosis (stage IV) also receive radiation; however, ongoing research continues to reduce the number of patients who require this modality.

1. Which of the following types of lymphoma has the best outcome when the duration of treatment is at least 2 years and includes a maintenance phase of therapy?

A. Stage IV anaplastic large-cell lymphoma

B. Burkitt leukemia (>25% blasts in marrow)

C. Stage III T-cell lymphoblastic lymphoma (LLy)

D. Stage IVB Hodgkin lymphoma

E. Stage III diffuse large B cell lymphoma

**Question 6**

**Answer:** C

Explanation

The distinction between lymphoblastic lymphoma (LLy) and acute lymphoblastic leukemia (ALL) is that the ALL is defined as more than 25% blasts in the bone marrow. The exact biologic distinction between these two entities is the subject of ongoing research. For stage III and IV LLy, results have been best when patients are treated with regimens like those used for ALL. These include maintenance phases with a total duration of therapy of at least 2 years. The other common pediatric lymphomas, even with extensive marrow involvement, are treated with less than 1 year of cyclic chemotherapy.

1. 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. A needle biopsy of one of these brain lesions will most likely reveal which of the following?

A. Lymphoblastic lymphoma

B. Bacterial abscess

C. EBV+ diffuse large B cell lymphoma

D. EBV+ Burkitt lymphoma

E. Glioblastoma multiforme

**Question 7**

**Answer:** C

Explanation: Primary CNS lymphoma is extremely rare in pediatric patients, so a work-up for immunodeficiency and HIV infection should be considered in any child diagnosed with primary CNS lymphoma. The risk of any lymphoma is greatly increased in any patient with T-cell compromise (HIV-infected, posttransplant patients, and children with inherited T-cell immunodeficiencies). Most lymphomas in immunodeficient patients are B-cell NHL and are often associated with EBV. Diffuse large B-cell lymphoma is the most frequent histologic subtypes.

1. A 11-year-old male 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 prior to therapy. Which part of therapy is most likely to cause male infertility?

A. Alkylating agents

B. Radiation

C. Bleomycin

D. Corticosteroids

E. Anthracycline

**Question 8**

**Answer:** A

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, procarbazine, etc., are very gonadotoxic to males and can result in azoospermia and infertility depending on the dose. In contrast, female infertility is more strongly associated with radiation (though oophoropexy can be performed to spare some of the radiation effect). Compared with females, 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 in males.

Alkylating agents and/or topoisomerase II inhibitors have been associated with secondary leukemias and myelodysplasia (MDS). Radiation has been associated with thyroid, skin, and breast cancer (particularly in adolescent females 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.

1. A 12-year-old male 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. Additional studies will 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

**Question 9**

**Answer:** A

Explanation: The patient has an anaplastic large cell lymphoma (ALCL), a mature T cell lymphoma. The majority of ALCL 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 or lambda immunoglobulin light chain gene locus t(8;22)(q24;q11). Although approximately one-third of pediatric DLBCL 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 as well as CD10. Although some DLBCL 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.

1. 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

**Question 10**

**Answer:** B

Explanation: Tumor lysis syndrome occurs when renal function cannot sufficiently eliminate the by-products 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 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 24–72 hours following initiation of therapy. However, bulky, rapidly growing tumors like Burkitt lymphoma or LL 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.

1. A 3-year-old female 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 EBV-positive monomorphic posttransplant lymphoproliferative disease (PTLD). The most appropriate initial treatment at this point is

A. Immunotherapy with a monoclonal antibody against CD20

B. Ganciclovir and intravenous immunoglobulin

C. B-cell NHL therapy for stage III disease

D. Reduction of immunosuppression

E. Low-dose chemotherapy such as cyclophosphamide and prednisone

**Question 11**

**Answer:** D

Explanation: PTLD occurs in 5%–10% of children undergoing organ transplantation. The majority (>70%) will be 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, though less frequently it resembles Burkitt lymphoma or even Hodgkin lymphoma. The disease can be polyclonal or monoclonal. Reduction of immunosuppression is usually 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 those patients who do not respond to reduction of immunosuppression, low-dose chemotherapy or immunotherapy can achieve durable remission in about two-thirds of patients.

1. An 8-year-old male 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

**Question 12**

**Answer:** C

Explanation: Lymphomas involving the ileocecal region in children are almost always Burkitt (or Burkitt-like). Sporadic Burkitt lymphoma commonly presents as an abdominal mass is boys 5–10 years of age. Clinically, they can present with abdominal pain, distention, emesis, gastrointestintal 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

1. An 8-year-old male presents with severe abdominal pain, vomiting, gastrointestinal bleeding, and fever. Abdominal ultrasound was suggestive of 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 neck, chest abdomen, and pelvis; and PET scan revealed no other sites of disease. According to the St. Jude (Murphy) staging system, the most appropriate stage for this patient is

A. Stage I

B. Stage II

C. Stage III

D. Stage IV

**Question 13**

**Answer:** B

Explanation: A primary gastrointestinal tract NHL that is resectable (as in the case above) is stage II, according to the St. Jude (Murphy) staging system (detailed in a previous question), 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.

1. A 12-year-old female presents with 6 months of red-to-brown raised skin lesions that become hemorrhagic, crusted, and disappear after 3–4 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’s disease

B. Burkitt’s lymphoma

C. DLBCL

D. LL

E. ALCL

**Question 14**

**Answer:** E

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, can be very difficult to distinguish from lymphomatoid papulosis. Clinical symptoms in ALCL are quite variable with B symptoms being more common than in other NHL. The pathologic diagnosis can be difficult to make. Immunophenotyping can be helpful because all ALCL will express CD30, differentiating it from DLBCL, but most Hodgkin’s disease is CD30(+). CD45 is helpful in distinguishing between ALCL, which is CD45(+), and HD, 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.

1. A 4-year-old male 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. FISH testing for MYC translocations are 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

**Question 15**

**Answer: B**

Explanation: nLPHL is a B cell lymphoma that is significantly different from Hodgkin lymphoma. nLPHL accounts for 10%–20% of pediatric Hodgkin lymphoma; usually presents with early stage disease (IA, IIA); has a male predominance, indolent course, and good prognosis; but can have late and occasionally multiple relapses. The malignant cells of nLPHL are LP cells (formerly known as L&H [lymphocytic & 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 (BOB.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%–50% of cases. Patients with Burkitt lymphoma have translocations t(8;14)(q24;q32) in 70%–80% and t(2;8)(p12;q24) or t(8;22)(q24;q11) in 10%–15% of patients. These translocations involve the cMYC oncogene and the immunoglobulin heavy chain, κ light chain or λ immunoglobulin light 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.

16. A 4-year-old male presents with a 6-week history of progressive submandibular lymphadenopathy. Excisional biopsy of a 3-cm lymph node reveals nodular lymphocyte-predominant Hodgkin lymphoma (nLPHL). He has no B symptoms, and PET and CT imaging show no additional lymphadenopathy or focus of disease. Which of the following describes the most reasonable treatment approach for this patient?

A. Close observation for recurrence

B. 3 to 4 cycles of multiagent chemotherapy

C. Immunotherapy targeting CD30

D. 4 to 6 cycles of multiagent chemotherapy followed by involved field radiation therapy

E. A and B are appropriate.

F. A, B, and C are appropriate.

**Question 16**

**Answer:** E

Explanation

Nodular lymphocyte-predominant Hodgkin lymphoma (nLPHL) is a mature B cell lymphoma that is significantly different from classic 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. This patient has stage IA disease (single lymph node, no B symptoms), and the tumor has been completely excised. Many patients with stage IA nLPHL can be cured with surgery alone, and when relapses do occur, they also tend to be low stage and are responsive to multiagent chemotherapy yielding high overall survival rates. Thus, clinical observation is a reasonable option. Because recurrence following complete resection occurs in approximately 20% to 25% of nLPHL patients, it is reasonable to give give 3 to 4 cycles of adjuvant multiagent chemotherapy. Such regimens induce complete remission in more than 90% of incompletely resected low-stage disease and would therefore be expected to improve event-free survival in the adjuvant setting. However, in patients with completely resected disease, providers must weigh the potential benefit of improved outcomes with the risk of late effects of chemotherapy. In low-stage nLPHL, radiation therapy generally is reserved for patients with inadequate response to chemotherapy. In this patient, whose disease has been completely resected, chemotherapy followed by radiation would be excessive and would result in more toxicity than benefit. Classic Hodgkin lymphomas typically are positive for CD30, and immunotherapy targeting this surface molecule has yielded excellent response rates in clinical trials. In contrast, nLPHL typically is negative for CD30; therefore, this immunotherapy would not be appropriate.

17. A 2-year-old male 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, serum chemistries—including uric acid and LDH—were normal. CT imaging showed extensive, bulky lymphadenopathy with mild adjacent inflammatory stranding within 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 upon 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. nLPHL

C. Langerhans cell histiocytosis

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

E. Infectious mononucleosis

F. ALCL

**Question 17**

**Answer:** D

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 germial centers, and Castleman disease. Autoimmune diseases also can present with significant lymphadenopathy.

18. A 5-year-old male 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

**Question 18**

**Answer:** A

Explanation: This patient has stage III Burkitt lymphoma as indicated by diffuse abdominal involvement. NHL are staged according to the St. Jude (Murphy) system. High LDH is a negative prognostic feature in Burkitt lymphoma in both Berlin-Frankfurt-Munster (BFM) and French American British Society of Pediatric Oncology (FAB/LMB) trials. Elevated uric acid is indicative of 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. C-MYC 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 ~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 have 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.

19. A 13-year-old female 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. FDG-PET shows increased uptake in the cervical nodes and mediastinal mass only. CT shows cervical and supraclavicular lymphadenopathy involving 2 nodal groups with the largest nodal aggregate measuring 4 cm in the longest transverse diameter. There is no additional lymphadenopathy, hepatosplenomegaly, splenic nodules, or focal defects. The patient most likely has

A. Low-risk classical Hodgkin lymphoma

B. Low-risk classical nodular lymphocyte predominant Hodgkin lymphoma

C. Low-risk anaplastic large cell

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

**Question 19**

**Answer:** A

Explanation: This patient stage IIA, nonbulky, mixed cellularity, classical Hodgkin lymphoma and is considered low risk.

The malignant cell of classical Hodgkin lymphoma is the Reed-Sternberg cell (described above). The malignant cell of nLPHL is the LP cell, a mononuclear variant of the HRS cell, generally has a convoluted irregular nucleus and several small nucleoli (sometimes referred to as “popcorn cells”). Classical Hodgkin lymphoma tend to stain positive for CD15 and CD30 but are negative for CD45 whereas nLPHL stain positive for CD45 but are negative for CD15 and CD30. Classic Hodgkin lymphoma is more common that nodular lymphocyte predominant Hodgkin lymphoma 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 non-mediastinal nodal aggregative is <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 has been abandoned long ago. Although the major pediatric cooperative oncology consortia vary in their risk stratification of Hodgkin lymphoma, non-bulky stage IIA is nearly always low risk.

Staging for advanced Hodgkin lymphoma often involves bilateral bone marrow biopsies and aspirates. However, recent data have suggested that PET/CT has greater sensitivity and specificity for detecting bone marrow disease than bone marrow biopsies and aspirates. Given 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 upstage 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 currently is under investigation.

20. A 13-year-old female with no history of immune deficiency presented with shortness of breath, abdominal distension, abdominal pain, and urinary frequency and urgency. Imaging revealed abdominal mass, ascites, and pleural effusions. Pleural fluid aspirate was positive for diffuse large B-cell lymphoma (DLBCL). Her central nervous system (CNS) and marrow were not involved. After three cycles of chemotherapy, follow-up imaging studies showed her to be in complete remission with no evidence of disease. Following the completion of therapy, what is the appropriate off-therapy follow-up for this patient?

A. PET imaging of the chest, abdomen, and pelvis at regular intervals for 1 year

B. PET imaging of the chest, abdomen, and pelvis at regular intervals for 2 years

C. PET imaging of the chest, abdomen, and pelvis at regular intervals for 5 years

D. None of the above

**Question 20**

**Answer:** D

Explanation

PET and PET-CT are used to diagnose, stage, and monitor how well treatment is working. Available evidence from clinical studies suggests that using PET or PET-CT to monitor for recurrence does not improve outcomes and therefore generally is not recommended for this purpose. False-positive PET-CT tests can lead to unnecessary and invasive procedures, overtreatment, unnecessary radiation exposure, and incorrect diagnoses. Off-therapy follow-up for patients with pediatric Hodgkin and non-Hodgkin lymphoma should include medical history and physical examination at regular intervals to evaluate for possible recurrence.

Although not a specific content specification, surveillance CT imaging for patients who have completed therapy is controversial. While many oncologists use surveillance CT imaging at regular intervals following completion of therapy, there is no proven survival benefit from routine surveillance imaging over clinical surveillance. In the absence of concerning signs, symptoms, or laboratory abnormalities, additional imaging for patients who have obtained a complete response while on therapy may not be indicated. Monitoring for late effects of chemotherapy should be performed according to evidence-based guidelines.

21. A 6-year-old male presents with rapidly increasing abdominal girth, abdominal pain, 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, he is currently at immediate risk of which of the following:

A. Tumor lysis syndrome

B. Superior vena cava syndrome

C. Superior mediastinal syndrome

D. Spinal cord compression

E. Intestinal perforation

**Question 21**

**Answer:** A

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 mostly frequently males aged 5-10 who present with nausea, vomiting, abdominal pain or distension, and GI bleeding. Intestinal perforation can occur, but is rare. Even prior to the initiation of chemotherapy, patients with high grade Burkett leukemia/lymphoma are at high risk of spontaneous tumor lysis syndrome. Risk factors include large tumor burden, elevated LDH, and renal involvement of disease. While prophylaxis with recombinant xanthine oxidase reduces this risk, it remains greater than 10% of cases. While Burkitt lymphoma can involve the mediastinum, presentation in this location is very rare.

22. A 12 year old male presents with 2 weeks of cough, fatigue, dyspnea, dysphagia, chest pain, low grade fevers and an 8 pound 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. The most likely diagnosis is

A. Primary Mediastinal B cell lymphoma

B. Anaplastic Large Cell lymphoma

C. Nodular Sclerosing Hodgkin Lymphoma

D. T cell lymphoblastic lymphoma

**Question 22**

**Answer:** D

Explanation: This is classic presentation for T cell lymphoblastic lymphoma. Lymphoblastic lymphoma accounts for approximately 20% of pediatric NHL. Approximately 75% of lymphoblastic lymphomas are T lineage, and 90% are stage III-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, however this entity is much less common and accounts for only 1-2% of pediatric NHL

23. A 17 year old male presents with 2 weeks of worsening fatigue, cough, and shortness of breath. The 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. The most appropriate next step is:

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

**Question 23**

**Answer: B**

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 of the pleural effusion via a thoracentesis will likely alleviate his respiratory symptoms and the pleural fluid may contain sufficient material for diagnosis. Bone marrow biopsy, although also relatively non-invasive, may or may not yield the diagnosis in the presence of a normal CBC, and will not relieve the patient’s symptoms. Intubation of a patient with a mediastinal mass is inappropriate as 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, as it requires greater sedation than a thoracentesis is incorrect as the first step. Empiric therapy with either steroids or radiation to the mediastinal mass are 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.

24. A 13-year-old female 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. The most likely diagnosis is

1. Classical Hodgkin lymphoma
2. Nodular lymphocyte predominant Hodgkin lymphoma
3. Anaplastic large cell lymphoma
4. Burkitt lymphoma
5. Diffuse large B cell lymphoma

**Question 24**

**Answer: E**

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

25. A 17-year-old male presents with progressive cervical lymphadenopathy. An incisional biopsy is performed, and the tumor is shown to express genetic material from the Epstein-Barr virus (EBV). Which of the following diagnoses is *least* likely to be associated with EBV?

A. Nodular lymphocyte predominant Hodgkin lymphoma

B. Nodular sclerosing Hodgkin lymphoma

C. Lymphocyte depleted Hodgkin lymphoma

D. Sporadic Burkitt lymphoma

E. Endemic Burkitt lymphoma

F. Anaplastic large-cell lymphoma

G. T-cell post-transplant lymphoproliferative disorder (PTLD)

**Answer: F**

The World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissue, 2008 edition, states that anaplastic large-cell lymphoma (ALCL) is “consistently negative for Epstein-Barr virus (EBV)” (although case reports exist in the medical literature).

EBV is an exclusively human pathogen and was the first oncogenic virus recognized. It is responsible for both lymphatic and epithelial tumors. Approximately 95% of the population worldwide are serologically positive for EBV, which persists as a life-long asymptomatic latent infection in B cells. Viral reactivation has been linked to oncogenesis in some cases of Burkitt lymphoma, Hodgkin lymphoma, B-cell and T-cell post-transplant lymphoproliferative disorders (PTLD), and T-cell lymphomas. The frequency of EBV expression in Hodgkin and non-Hodgkin lymphomas are below:

Lymphoma % associated with EBV

Anaplastic large cell lymphoma ~0%

Nodular lymphocyte predominant Hodgkin lymphoma <5%

Sporadic Burkitt lymphoma 15%

Nodular sclerosing 25%

T-cell PTLD 30%

Lymphocyte predominant Hodgkin lymphoma 42%

Mixed cellularity Hodgkin lymphoma 75%

B-cell PTLD 80%

Endemic Burkitt 95%

Lymphocyte depleted Hodgkin lymphoma 100%

26. A 15-year-old female presents with stage IIIB, nodular sclerosing Hodgkin lymphoma involving thoracic and abdominal lymph nodes. PET imaging shows no other sites of disease. Following 2 cycles of chemotherapy her lymph nodes have all decreased in size and with the largest nodal aggregate deceasing from 13 cm in its longest axis to 6 cm. Her imaging remains mediastinal mass has reduced in diameter by half. Her tumor remains PET-AVID with maximal standard uptake values (SUV) in the nodal aggregate of 2.1 compared with 2.8 in the mediastinum. Her response to therapy should therefore be considered:

A. Complete metabolic response

B. Partial response

C. Stable disease

D. Refractory disease

**Answer: A**

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.

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

A Deauville score of 1-3 is generally accepted and a 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, 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.

27. A 15-year-old female presents with 1 week of fatigue, nausea, headaches, diffuse myalgias. CBC with automated differential revealed anemia (hgb 8.9g/dl), thrombocytopenia (plt 132,000/ul), an WBC of 49,000 and differential showing 58% neutrophils, 7% band cells, 38% lymphocytes, 3% monocytes. Imaging shows hematosplenomegaly and and prominent cervical, abdominal, pelvic lymph nodes. There is no mediastinal mass. Testing for EBV and 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 neucleoli, and abundant cytoplasm. Cells stain negative for CD3, CD4, CD8 and TdT but are positive for CD7. You are concerned this patient may have:

A. T-lymphoblastic leukemia

B. T-lymphoblastic lymphoma

C. Anaplastic large cell lymphoma

D. B-lymphoblastic leukemia

E. Diffuse large B cell lymphoma

**Answer: C**

Bone marrow biopsy confirmed ALK+ small cell variant anaplastic large cell lymphoma (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 a mature T cell lymphoma, 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 due to the process of making the peripheral smear. It is not uncommon for an automated differential to miss malignant ALCL cells.

28. You have a 7-year-old male treated for a hematolymphoid malignancy relapse 10 months after completion of therapy. Which primary diagnosis carries the *least* favorable outcome at relapse?

A. Average risk B-lymphoblastic leukemia

B. Stage III B-lymphoblastic lymphoma

C. Stage IIIA Hodgkin lymphoma

D. Stage III anaplastic large-cell lymphoma

**Answer: B**

Based on published consortium trials, patients with stage III to IV B-lymphoblastic lymphoma have cure rates ranging from 80% to 95% when treated with standard chemotherapy. However, prognosis following relapse is abysmal. In contrast, the remaining diseases can often be cured with standard chemotherapy, which may or may not include autologous or allogeneic hematopoietic stem cell transplantation. In addition, several novel therapies (including small molecule inhibitors, naked antibodies, antibody drug conjugates, bispecific antibodies, or chimeric antigen receptor T-cells) have been shown to be highly active in the other diseases. Whether novel agents improve survival in relapsed B-lymphoblastic lymphoma remains to be seen.

29. A 3-year-old male presents to your office witch 4 x 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, nuclear TdT. The diagnosis of B-lymphoblastic lymphoma is made. In this patient, which clinical feature confers a significant increased risk of relapse?

1. Age at diagnosis
2. White blood cell count <10,000 at diagnosis
3. Hyperdiploid cytogenetics
4. Extranodal (Skin) involvement

**Answer: A**

Unlike acute lymphoblastic leukemia in which patients greater than 10 years of age at diagnosis, in B lymphoblastic lymphoma, patients less than 4 years at diagnosis have a significantly higher risk of relapse (~45%) compared with children 4-15 years of age (~5%). Currently white blood cell count and hyperdiploid cytogenetics are not used risk stratification. Skin is involved in ~37% of cases of B-Lymphoblastic lymphoma and is not prognostic.

30. A 16-year-old male female presents to your office with diffuse supraclavicular, cervical, and axillary lymphadenopathy which has been progressing over the past two weeks. Imaging also reveals an anterior mediastinal mass and small pleural effusion. She has no cough, respiratory distress, airway or tracheal compression. She completed therapy for lymphoma 13 months prior 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 prolonged second remission with limited therapy minimal toxicity

1. B-lymphoblastic lymphoma
2. Diffuse large B cell lymphoma
3. Burkitt lymphoma
4. T lymphoblastic lymphoma
5. Anaplastic large cell lymphoma

**Answer: E**

Relapsed B cell non-Hodgkin lymphomas (B-lymphoblastic lymphoma, Diffuse large B cell lymphoma) all have very poor prognosis, and require multiagent high dose chemotherapy and stem cell transplant for cure. T lymphoblastic leukemia and T lymphoblastic lymphoma have similarly poor prognosis. In contrast, 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). While sustained remission has been reported, the optimal duration of treatment with such agents, and the likelihood of cure with such minimal therapy has yet to be determined.

31. A previously healthy 7-year-old male presents to his primary care doctor with fatigue, dyspnea on exertion, orthopnea, headaches, and cough, which have been progressive over the past 2 weeks. On examination, he is anxious, tachypneic, has facial edema and swelling, and distended neck veins. Chest x-ray reveals a large anterior mediastinal mass with no pleural or pericardial effusion. You are most concerned that his symptoms are due to what complication of newly presenting lymphoma?

1. Tumor lysis syndrome
2. Pulmonary leukostasis
3. Superior vena cava syndrome
4. Superior mediastinal syndrome

Answer: D

Superior vena cava (SVC) syndrome is compression and obstruction of the SVC resulting in impaired venous return. This occurs with anterior mediastinal masses because the SVC has a thin wall, low intraluminal pressure, and is anatomically surrounded by the thymus in other lymph nodes. Superior mediastinal syndrome is SVC syndrome with airway compromise, which is the case with this patient. The trachea and mainstem bronchi are more compliant and compressible in children compared with adults. Some signs of respiratory compromise are evident in up to 75% of patients presenting with a new anterior mediastinal mass. Signs of airway compromise include cough, hoarseness, tachypnea, dyspnea, orthopnea, stridor, wheezing, and anxiety. Signs of venous obstruction include swelling; plethora; cyanosis of the face, neck, and upper extremities; engorgement of chest wall vessels; petechiae of the head, neck, arms, and trunk; edema; pleural effusions; and pulsus paradoxus. Patients may also have central nervous system signs including headache, confusion, lethargy, blurry vision, papilledema, syncope, and a sensation of fullness in their ears.

32. A previously healthy 17-year-old male presents with several weeks of progressive shortness of breath, fatigue, cough, and orthopnea. Imaging reveals a large anterior mediastinal mass but no other foci of disease. Biopsy reveals a primary mediastinal B-cell lymphoma (PMBCL). He is started on conventional therapy. Which of the following therapies represent rational therapeutic targets for this disease?

1. A high specific antibody that targets CD3 and CD19
2. A monoclonal antibody targeting CD20
3. A monoclonal antibody drug conjugate targeting CD30
4. Monoclonal antibodies targeting either PD-L1, or PD-L2
5. All of the above

Answer E

Each of these agents, or class of agents, has the potential to be active in this disease. Primary mediastinal B-cell lymphoma (PMBCL) is a rare thymic B-cell lymphoma comprising only about 1% of pediatric non-Hodgkin lymphomas. Its gene profile overlaps with classic Hodgkin lymphoma in that the two entities share approximately one-third of genes. Its phenotype consists of B-cell markers including CD 19, CD20, CD22, CD79, and CD30 in approximately 80% of cases and PD-L1 or PD-L2 in approximately 70% of cases. Blinatumomab is a bi-specific antibody that targets CD3 and CD19, is very active against relapsed acute lymphoblastic leukemia, and may have a future role in relapsed CD19 positive non-Hodgkin lymphoma. Rituximab is an anti-CD20 monoclonal antibody, which is part of standard upfront therapy for pediatric CD20-positive non-Hodgkin lymphomas. Brentuximab vedotin is an antibody to CD30 that is conjugated to the microtubule inhibitor monomethyl auristatin E and may be active in some patients with PMBCL. Checkpoint inhibitors target programmed cell-death receptors or their ligands and disrupt inhibitory signals from tumors against tumor infiltrating lymphocytes and can restore antitumor immunity.

33. A previously healthy 17-year-old male presents with several weeks of progressive shortness of breath, fatigue, cough, and orthopnea. Imaging reveals a large anterior mediastinal mass, but no other foci of disease. Biopsy reveals a primary mediastinal B-cell lymphoma (PMBCL). He is started on conventional therapy using dose-adjusted EPOCH with rituximab. At the end of six cycles of chemotherapy, PET-MRI shows approximately 80% reduction in the size of the mass; however, there is a small 1.5-cm focus of residual PET-avid disease (Deauville 4). What is most appropriate next step?

1. Repeat PET-MRI in several months
2. Core needle biopsy
3. Excisional biopsy
4. Radiation to the residual PET-avid disease
5. High-dose chemotherapy followed by autologous bone marrow transplant
6. High-dose chemotherapy followed by allogeneic bone marrow transplant

Answer: A

Fluorodeoxyglucose (FDG)-PET is routinely performed at the completion of chemoimmunotherapy in primary mediastinal B-cell lymphoma (PMBCL) to assess remission status. A negative PET scan is defined by FDG uptake less than or equal to uptake in the liver (Deauville score 1-3). Although it is true that patients with a negative end-of-therapy (EOT) PET scan have been found to have improved outcomes in prospective and retrospective series, most patients with PET-avid (Deauville 4) residual lesion do not have relapse of their disease. Therefore, a small PET-avid residual lesion could also be due to post-treatment inflammatory tissue in the mediastinum, which results in a high rate of false positive results.

34. A 4-year-old male presents with a week of progressive abdominal distention. Imaging reveals diffuse abdominal lymphadenopathy and ascites. A CBC is normal. A metabolic panel shows hyperuricemia, hyperphosphatemia, and elevated creatine but normal potassium. A paracentesis is performed, and the peritoneal fluid is positive for malignant cells, which contain an IgH-MYC translocation. Immediate management strategies will include which of the following (there is more than 1 correct answer)?

1. Hyperhydration
2. Alkalinization with sodium bicarbonate
3. Uric acid reduction with either a xanthine oxidase inhibitor or recombinant urate oxidase
4. Low-intensity chemotherapy to reduce tumor burden and prevent tumor lysis
5. Intensive multiagent chemotherapy with the goal of rapid remission induction

Answers: A, C, D

The patient has Burkitt lymphoma, which is at least stage 3 due to diffuse abdominal involvement. Burkitt lymphoma is a highly aggressive tumor with the capacity to double in size overnight, placing this patient at high risk of spontaneous, life-threatening tumor lysis syndrome (TLS). Prophylactic measures for patients at risk of TLS include aggressive fluid management and judicious use of diuretics and hypouricemic agents. Both allopurinol and urate oxidase are effective in reducing serum uric acid. Allopurinol should be used as prophylaxis in low-risk cases and urate oxidase should be used as treatment in intermediate- to high-risk cases. The routine use of diuretics and urine alkalinization are not recommended. This patient already has evidence of spontaneous tumor lysis and a high disease burden, so a reduction phase with lower intensity chemotherapy designed to reduce tumor burden without inducing fulminant tumor lysis is appropriate. The patient will require further evaluation to determine if there is marrow or central nervous system involvement; however, managing the patient’s TLS is the most immediate priority.

35. A 4-year-old male 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. Excisional biopsy is performed, which shows nodular lymphocyte predominant Hodgkin lymphoma, stage IA. Staging workup reveals no additional sites of disease. Because his disease appears to have been completely surgically resected, he is treated with observation only (no chemotherapy). Nine months after surgery, he develops supraclavicular lymphadenopathy. The node is approximately 3.5 cm in diameter, firm, and fixed. What is the next step in therapy?

1. PET-CT or PET-MRI and treat with chemotherapy based on staging of recurrence
2. PET-CT or PET-MRI and treat with involved-node radiation therapy
3. Excisional biopsy
4. Ultrasound of the lymph node
5. None of the above

Answer: C

In pediatrics, nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) typically presents in young males with localized disease and no systemic symptoms. Low-stage disease that is completely resected does not necessarily require systemic chemotherapy and can be followed clinically. A subset of these patients will relapse and require systemic chemotherapy. The patient’s physical examination meets criteria for pathologically enlarged lymphadenopathy concerning for malignancy, which is unlikely to be ruled out by an ultrasound of this supraclavicular node. Although it is most likely that this patient has relapsed NLPHL, a subset of patients with NLPHL can transform to diffuse large B-cell lymphoma. The frequency of transformation in pediatrics is not well established because of the rarity of its occurrence, but, in adult series, transformation can occur in between 15% and 25% of cases. Therefore, a biopsy to confirm relapse rather than transformation is warranted prior to starting new therapy.