

Educational Case: Burkitt Lymphoma

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*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289519884733>.*¹

Keywords

pathology competencies, organ system pathology, hematopathology, white cell disorders, lymph nodes, lymphoma, pediatric, Burkitt lymphoma

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Primary Objective

Objective HWC3.6: Hodgkin and Non-Hodgkin Lymphoma: Compare and contrast Hodgkin lymphoma with at least 2 non-Hodgkin lymphomas with respect to age and clinical symptoms at presentation, sites and pattern of spread of disease, cell of origin histologic appearance, and prognosis and response to therapy.

Competency 2: Organ System Pathology; Topic Hematopathology: White Cell Disorders (HWC); Learning Goal 3: Classification of Leukemia and Lymphomas.

Secondary Objectives

Objective HWC4.3: Staging of Hematolymphoid Neoplasia: Define staging as it applies to lymphoma and give examples of different lymphomas in which staging has different clinical implications.

Competency 2: Organ System Pathology; Topic Hematopathology: White Cell Disorders (HWC); Learning Goal 4: Clinical Features of Hematolymphoid Neoplasms.

Objective HWC3.3: Categories of Lymphoma: Compare and contrast low-grade or indolent lymphomas and high-grade or aggressive lymphomas with respect to underlying pathophysiology that yields specific morphologic features and clinical behavior.

Competency 2: Organ System Pathology; Topic Hematopathology: White Cell Disorders (HWC); Learning Goal 3: Classification of Leukemia and Lymphomas.

Patient Presentation

A 5-year-old previously healthy male initially presented to the emergency department with right-sided Bell's palsy and slurred speech. There was no history of trauma. A computed tomogram of the head was negative for signs of stroke, and he was discharged with a prescription for steroids. On follow-up with his pediatrician, he was noted to have a white blood cell (WBC) count of 12.9 K/ μ L (normal: 5-14.5 K/ μ L).² The patient's younger brother was recently diagnosed with influenza. The patient's rapid influenza test was negative, but his symptoms were presumed to be due to infection and he was prescribed Augmentin. He was seen 2 weeks later with progressive weakness, abnormal gait, arm pain, weight loss, and depressed

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mood. The pediatrician noted absent lower extremity reflexes and advised the patient to go to the emergency department.

Diagnostic Findings, Part 1

In the emergency department, vital signs are evaluated and found to be normal. A complete blood count shows a WBC count of 9.4 K/ μ L (normal: 5-15.5 K/ μ L), hemoglobin of 12.9 g/dL (normal: 11.5-13.5 g/dL), hematocrit of 37.3% (normal: 34%-40%), and platelet count of 324 K/ μ L (normal: 150-350 K/ μ L).² Magnetic resonance imaging (MRI) of the brain and spinal cord shows leptomeningeal enhancement as well as enhancement of multiple nerves, including cranial nerves and nerve roots in the cervical and thoracic spine and cauda equina.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis for This Patient's Progressive Neurologic Symptoms?

The differential diagnosis for this patient's neurologic symptoms and imaging findings includes inflammatory central nervous system (CNS) disorders such as acute disseminating encephalomyelitis (ADEM) or Guillain-Barre syndrome (GBS), CNS vasculitis, primary metabolic disorders, infections such as viral encephalitis or Lyme neuroborreliosis, or neoplasms such as a solid CNS tumor or lymphoma.³

Acute disseminating encephalomyelitis is an acute autoimmune demyelinating disease on a spectrum with other demyelinating diseases such as multiple sclerosis and optic neuritis. It has an acute onset of symptoms which may include cranial nerve palsy, ataxia, and altered mental status. Although these symptoms are present in this case, in contrast to the diffuse leptomeningeal and nerve root enhancement seen on this patient's MRI, patients with ADEM typically have large asymmetric white matter lesions. Patients often receive treatment with intravenous steroids, although symptoms may take weeks to months to resolve.⁴

Guillain-Barre syndrome is an autoimmune disorder which presents with symmetric sensory and motor defects, which begin in the distal extremities and progress proximally. Patients often have a history of recent infection. Patients may benefit from steroids, although intravenous immunoglobulin or plasma exchange is often required.⁵ Although this patient did present with ataxia and loss of lower reflexes, he did not have progressive distal to proximal spread of symptoms typical for GBS.

Central nervous system vasculitis presents with nonspecific findings. Focal neurologic signs and behavioral change, as seen in this patient, may be present. Patients also often present with diffuse neurologic symptoms such as headache or seizures. Leptomeningeal and vascular wall enhancement may be seen on MRI. Treatment includes high-dose steroids.³

Neuroborreliosis and viral meningitis are less likely in this patient, as they would not explain his progressive focal neurologic deficits. Primary metabolic disorders include a broad range of diseases which may present with a variety of



Figure 1. Computed tomography shows a 4 cm soft tissue mass (outlined in red) adjacent to the tail of the pancreas (black arrowheads).

symptoms; however, these disorders are relatively rare and would not be at the top of the initial differential.

Diagnostic Findings, Part 2

Lumbar tap shows cerebrospinal fluid (CSF) total protein is 98 mg/dL (normal: 5-40 mg/dL) and CSF glucose is 38 mg/dL (normal: 40-80 mg/dL). A cell count of the CSF shows 189 WBCs (normal: 0-7 cells/ μ L), and 1 red blood cell (RBC) with a WBC differential of 93% lymphocytes, 6% monocytes, and 1% neutrophils (normal: 70% lymphocytes, 30% monocytes).⁶

Questions/Discussion Points, Part 2

Interpret the CSF Findings

A traumatic tap, with contamination from peripheral blood, may complicate interpretation of CSF results. However, the presence of only 1 RBC in the cell counts suggests a "clean" nontraumatic tap. The WBC count is elevated, which can occur in infection, malignancy, or inflammatory diseases. The lymphocyte predominance would suggest against a bacterial meningitis, which would have a neutrophil predominance. The protein is mildly elevated and the glucose is mildly decreased. These changes can be seen in a variety of conditions, including inflammatory disorders, malignancy, and infection, although infection often causes a greater increase in protein.⁶

Diagnostic Findings, Part 3

An infectious workup, including a CSF viral encephalitis panel, is negative. Flow cytometry, a technique which analyzes cell surface antigens, is positive and shows an abnormal monoclonal B-cell population with expression of CD19, CD20, bright CD38, and CD10. Whole body imaging with computed tomography shows a 4 cm soft tissue mass in the left upper quadrant of the abdomen (Figure 1). Positron emission tomography

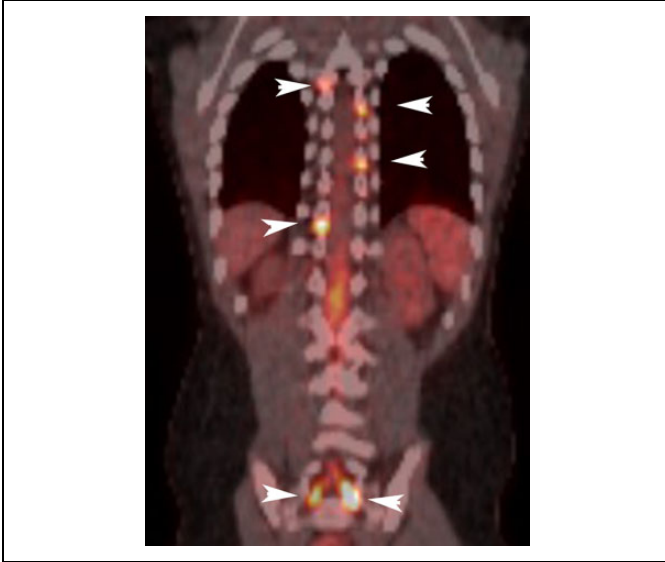


Figure 2. Bilateral enhancement and enlargement of nerve roots (white arrowheads) are seen at multiple levels including cervical (not pictured), thoracic, and lumbosacral on positron emission tomography.

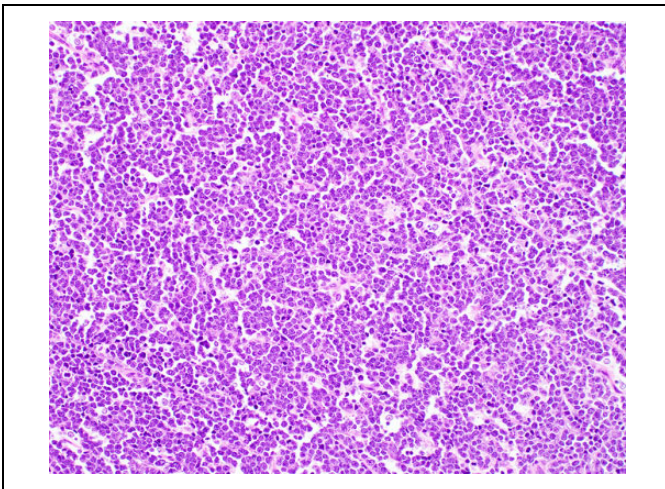


Figure 3. Sheets of atypical medium-sized monomorphic lymphocytes with frequent apoptotic bodies forming a “starry sky” appearance are characteristic of Burkitt lymphoma (H&E, $\times 200$ magnification). H&E indicates hematoxylin and eosin.

(PET), which uses a radioactive intravenous drug to identify areas of high chemical or metabolic activity, shows enhancement of the abdominal mass as well as enhancement of multiple nerve roots (Figure 2).

Questions/Discussion Points, Part 3

What Is the Differential Diagnosis Based on the Results of the Additional CSF Studies?

The positive flow cytometry result indicates that this patient has a B-cell lymphoproliferative disorder such as lymphoma or

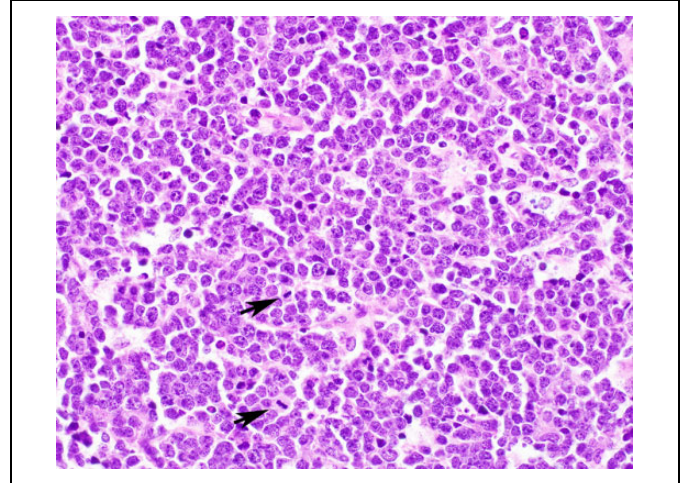


Figure 4. Higher power magnification shows round nuclei with clumped chromatin and multiple small nucleoli. Numerous mitotic figures (black arrowheads) and apoptotic bodies are present (H&E, $\times 400$ magnification). H&E indicates hematoxylin and eosin.

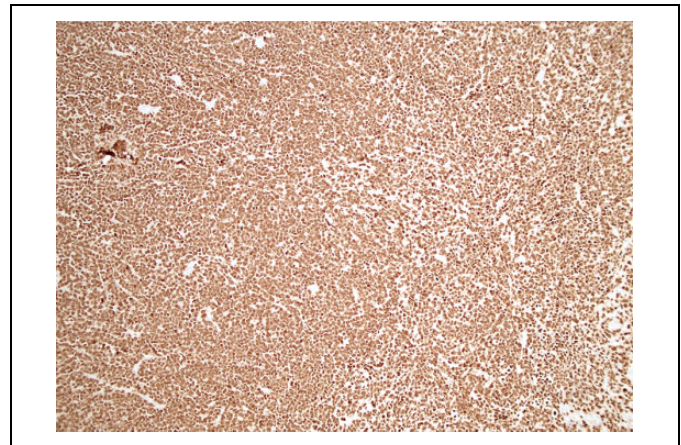


Figure 5. Mitotically active cells appear brown with Ki67 immunostaining. The Ki67 index approaches 100% in this case, meaning nearly 100% of cells are mitotically active (Ki67, $\times 100$ magnification).

leukemia. Many types of lymphoma such as diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma, as well as acute leukemias, can all present with CNS involvement.^{7,8}

Diagnostic Findings, Part 4

Biopsy of the abdominal mass reveals a proliferation of monomorphic medium-sized lymphoid cells with a high mitotic rate and abundant apoptotic bodies (Figures 3 and 4). Flow cytometric studies and immunohistochemical studies of the mass show that the tumor cells express CD20, BCL-6, and CD10 and are negative for BCL-2, CD34, and Tdt. The Ki67 proliferation index is near 100% (Figure 5). In situ hybridization studies for Epstein-Barr virus are negative. Fluorescent in situ hybridization analysis detected a MYC/IGH fusion in 75% of nuclei and was negative for rearrangements of BCL2 and BCL6.

Questions/Discussion Points, Part 4

What Is the Diagnosis Based on the Histologic, Flow Cytometric, and Molecular Findings?

The microscopic findings of a diffuse proliferation of monomorphic medium-sized mature lymphoid cells with a B-cell germinal center phenotype (CD10-positive, BCL6-positive) and a high proliferation index with a confirmed MYC/IGH translocation is consistent with a diagnosis of Burkitt lymphoma.

Describe the Microscopic Pathologic Features of Burkitt Lymphoma

Microscopically, the classic morphology for Burkitt lymphoma is diffuse sheets of monomorphic medium-sized B-cells. The nuclei are typically round with clumped chromatin and multiple small nucleoli. These tumors have a high mitotic rate with frequent apoptotic bodies. The low-magnification appearance of these tumors is often referred to as “starry sky” with the dense sheets of small blue lymphocytes forming the “sky” and scattered small white spaces filled with apoptotic debris forming the “stars.” On cytology aspirate smears, the abnormal cells have fine nuclear chromatin and basophilic cytoplasm with multiple lipid-containing vacuoles. The cell of origin for this lymphoma is a germinal center B-cell, and the tumor cells express B-cell antigens such as CD19, CD20, CD22, CD79a, and Pax5 as well as germinal center markers such as CD10 and BCL-6. The very high Ki67 proliferative index is characteristic of Burkitt lymphoma. The hallmark translocation associated with Burkitt lymphoma is the MYC-IGH fusion, t(8;14)(q24;q32), seen in this patient. Additional less common MYC translocations include t(2;8) and t(8;22).⁷ Alteration of the MYC proto-oncogene has numerous downstream effects including increased proliferation of B-cells and alterations in regulation during germinal center maturation.⁹

Describe the 3 Different Pathogenic Subtypes of Burkitt lymphoma

There are 3 subtypes of Burkitt lymphoma based on epidemiologic studies, including endemic Burkitt lymphoma, immunodeficiency-associated Burkitt lymphoma, and sporadic Burkitt lymphoma. All subtypes have an etiologic correlation with the Epstein Barr virus (EBV).⁷

The endemic variant is prevalent in areas of Equatorial Africa and Papua New Guinea and has a strong epidemiological link with malaria and EBV infection. It has a peak incidence between 4 and 7 years of age and has a male predominance. The facial bones, particularly the jaw, are the most common site of tumor involvement in endemic Burkitt lymphoma.⁷

Immunodeficiency-associated Burkitt lymphoma is most commonly associated with HIV infection. This association is still present in the era of highly active antiretroviral therapy, and the disease often presents early when the patient has high CD4 counts. Involvement of the lymph nodes and bone marrow

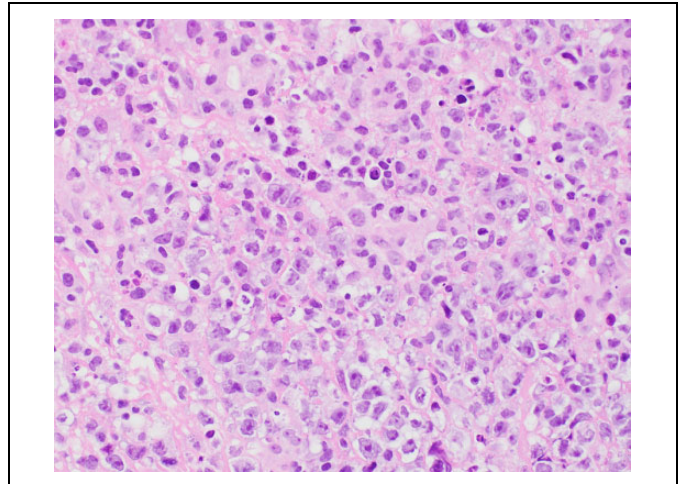


Figure 6. Sheets of large atypical lymphocytes are seen in diffuse large B-cell lymphoma (H&E, ×400 magnification). H&E indicates hematoxylin and eosin.

is more common in immunodeficiency-associated Burkitt lymphoma than in other variants.⁷

The sporadic variant of Burkitt lymphoma occurs worldwide. It is the most common variant in the United States, accounting for 30% to 50% of all childhood lymphomas. Sporadic Burkitt lymphoma primarily affects children and young adults and has a male predominance.⁸ The tumor most commonly presents as an abdominal mass. Central nervous system involvement is seen in 9% to 13% of cases.¹⁰

All subtypes of Burkitt lymphoma are highly aggressive with rapidly developing symptoms and a high tumor burden. Symptoms depend on the location of disease involvement. Despite the aggressive nature of Burkitt lymphoma, the disease is curable with long-term survival rates between 70% and 90%.^{7,8}

Describe Additional Types of Lymphoma Which May Occur in Childhood

Although typically seen in elderly patients with a median age in the seventh decade, DLBCLs may also present in children, accounting for 10% to 20% of pediatric non-Hodgkin lymphomas. Pediatric DLBCL is more common in patients between the ages of 10 and 20 years than in patients younger than 10 years.⁸ Lymph node involvement is common; however, the disease may occur anywhere, including the gastrointestinal tract, CNS, or mediastinum.^{7,8} B symptoms, such as weight loss, night sweats, and fever, are also common.¹¹ As the name implies, DLBCL shows a diffuse proliferation of large abnormal lymphoid cells that express B-cell antigens (Figure 6). In contrast to typical Burkitt lymphoma, the morphology of DLBCL is variable; nuclei may have vesicular chromatin with a single large nucleolus, as in the immunoblastic variant, or multiple nucleoli, as in the centroblastic variant, or may show bizarre pleomorphism as in the anaplastic variant. The most common gene rearrangement in DLBCL is translocation of the BCL6 gene. BCL2 and MYC translocations also occur, either

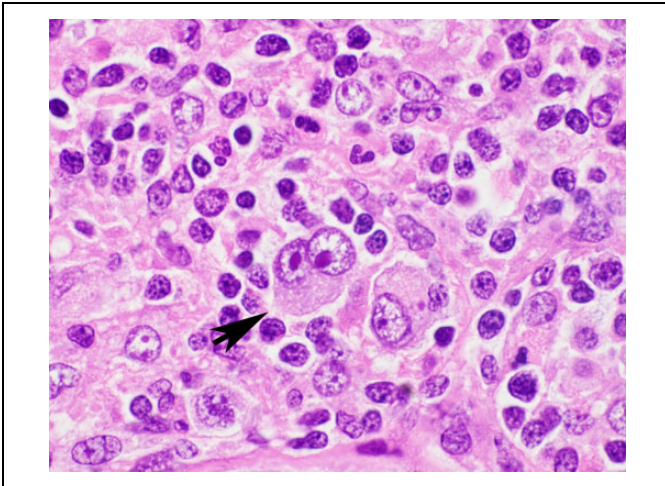


Figure 7. A Reed-Sternberg cell is seen here at high power (black arrowhead). Reed-Sternberg cells are large binucleated lymphocytes with prominent nucleoli and are characteristic of classic Hodgkin lymphoma (H&E, $\times 1000$ magnification). H&E indicates hematoxylin and eosin.

individually, or together, as in the so-called “double hit” or “triple hit” high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. Because there is histologic and genetic overlap between Burkitt and high-grade B-cell lymphomas and DLBCL, a diagnosis depends on the combination of morphologic, immunophenotype and genetic features, rather than one single diagnostic feature.⁷ Diffuse large B-cell lymphoma tends to behave aggressively, although the outcome depends on the subtype of disease and a variety of prognostic factors, including age. Although approximately 30% to 40% of patients overall will relapse following initial therapy, children typically have much better outcomes with long-term survival rates of 80% to 95% even in higher stage disease.^{8,11}

It is important to distinguish between a diagnosis of non-Hodgkin lymphoma and Hodgkin lymphoma for accurate treatment and prognosis. There are 2 main types of Hodgkin lymphoma: classic Hodgkin lymphoma (CHL) and nodular lymphocyte predominant (LP) Hodgkin lymphoma (NLPHL). Classic Hodgkin lymphoma has a broad age distribution, while NLPHL is most common among adults in the fourth and fifth decades.^{7,8} Patients with CHL typically present with cervical, mediastinal, and/or axillary lymphadenopathy, and approximately half of patients also have B symptoms.⁸ In contrast, patients with NLPHL tend to present with peripheral lymphadenopathy and rarely experience B symptoms.⁷ The hallmark microscopic feature for CHL is the Reed-Sternberg cell, a large binucleated cell with prominent eosinophilic nucleoli and abundant basophilic cytoplasm (Figure 7). Microscopically, Reed-Sternberg cells are present in varying numbers in an inflammatory background, which effaces the normal nodal architecture. The hallmark tumor cell in NLPHL is the LP cell, also called a “popcorn cell” due to its lobular nucleus surrounded by a thin rim of cytoplasm.⁷ Hodgkin lymphoma is curable, with 5-year survival rates over 98% in children.⁸

What Is the Stage of This Patient’s Disease?

The Ann Arbor Staging system is most widely used for both non-Hodgkin and Hodgkin lymphoma in children.⁸ Computed tomography is the most common imaging modality used in staging, although MRI and PET scanning are also useful to characterize the extent of disease. Stage I refers to involvement of a single lymph node or extranodal site, while stage II disease involves 2 or more lymph nodes on one side of the diaphragm or limited involvement of contiguous extranodal tissue. Involvement of lymph nodes or limited extranodal tissue on both sides of the diaphragm is classified as stage III. Stage IV is the highest stage and refers to diffuse or disseminated foci of extranodal involvement with or without lymphatic involvement. Each stage is further subdivided into A or B based on the absence (A) or presence (B) of B symptoms, including fever, weight loss, and drenching night sweats.^{8,12} This patient presented with an abdominal mass and multiple foci of CNS involvement with B symptoms (weight loss), making his disease Stage IVB.

Briefly Describe the Treatment Options for This Patient

Most pediatric patients with mature non-Hodgkin B-cell lymphoma have a good prognosis, regardless of stage. Multiagent chemotherapy is the mainstay of treatment; however, the protocol, including agents, dosages, treatment cycle duration, and number of cycles, may vary.^{8,10}

These patients are at risk for tumor lysis syndrome due to the high volume of tumor cells and high apoptotic rate. As the malignant cells begin to break down, the intracellular components including uric acid, potassium, and phosphorus are released. Normally, these components are filtered and excreted by the kidneys. However, in tumor lysis syndrome, the kidneys are overwhelmed by the large volume of dying cells, leading to the development of hyperuricemia, hyperkalemia, and hyperphosphatemia. Hyperhydration and treatment with allopurinol and rasburicase are used to combat these risks.⁸

Teaching Points

- Lymphomas are diagnosed pathologically by morphology, antigen expression as determined by immunophenotype and flow cytometry, and genetics.
- Burkitt lymphoma has a rapid onset of disease; however, symptoms vary widely based on the location of tumor involvement.
- There are 3 subtypes of Burkitt lymphoma—endemic, immunodeficiency associated, and sporadic. The sporadic variant is most common in the United States.
- The histology of Burkitt lymphoma shows sheets of monomorphic medium lymphocytes with a high mitotic rate and frequent apoptotic bodies, classically described as a “starry-sky” appearance.
- Translocation of the MYC gene, typically t(8;14), is a hallmark of Burkitt lymphoma. However, MYC rearrangements can also be seen in DLBCL.

- Staging of lymphoma relies primarily on radiographic findings and is determined by the location and extent of tumor involvement.
- Lymphoma is not a surgically resectable disease. Treatment primarily involves chemotherapy.
- Although children with mature B-cell lymphomas typically have good outcomes following treatment, they are at risk of tumor lysis syndrome due to high tumor burden. Additional therapy is required during treatment to mitigate this risk.

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