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Approach to Pediatric Lymphoma

Developed by Emily Allin and Dr. Brenna Eldridge for PedsCases.com.
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Introduction

Hello everyone, my name is Emily Allin and I am a third-year medical student at the University of British Columbia. This podcast has been created in collaboration with Dr. Brenna Eldridge, who works as a pediatrician at the Kootenay Boundary Regional Hospital in Trail, BC. Dr. Eldridge completed her pediatric residency at Miami Children's Hospital, and a fellowship in hematology/oncology at the University of Utah.

In this approach to pediatric lymphoma, we endeavor to communicate the following learning objectives:

1. Define Hodgkin and Non-Hodgkin Lymphoma, and their various subtypes.
2. Review the epidemiology and prognosis of pediatric lymphoma.
3. Recognize the clinical presentation of pediatric lymphoma as well as oncologic emergencies.
4. Discuss the treatment of pediatric lymphoma as well as side effects of treatment.

Case Opener

A 7-year-old boy, Peter, and his mother have come into your pediatric office. The mother tells you that she is concerned as her son has had a small "ball" in his neck. She tells you it has been there for at least a month and hasn't gone away. They decided to come see you today as the mass may have grown.

Hodgkin and Non-Hodgkin Lymphoma

Lymphomas are cancers that develop from the malignant transformation of lymphoid cells. Lymphoid cells are found in primary lymph organs, such as the bone marrow and thymus, as well as secondary lymph organs such as lymph nodes, spleen, and mucosa-associated lymphoid tissue (MALT).

Lymphoma is divided into two distinct clinicopathologic categories: Hodgkin and Non-Hodgkin lymphoma, each of which are further divided into subtypes. Hodgkin and Non-Hodgkin lymphoma have distinct clinical presentations and treatments.

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The World Health Organization classifies Hodgkin Lymphoma into Classical Hodgkin Lymphoma and Nodular Lymphocyte Predominance¹. The hallmark of classical Hodgkin lymphoma is the presence of **Reed-Sternberg cells**, detected from excisional biopsy of an enlarged lymph node. Reed-Sternberg cells are malignant cells that originate from B cells. The most common subtype of classic Hodgkin lymphoma, accounting for seventy percent of Hodgkin lymphoma, is Nodular Sclerosis. Nodular Sclerosis is more common in children older than ten years old. Other subtypes of Classical Hodgkin lymphoma include: Mixed Cellularity (more common in children younger than ten), Lymphocytic Rich and Lymphocytic Depletion lymphoma. The hallmark of Non-Classical Hodgkin Lymphoma, also called Nodular Lymphocyte Predominance Lymphoma (NLPHL), are **popcorn cells**. Non-Classical Hodgkin Lymphoma affects males more than females and accounts for ten percent of all Hodgkin Lymphoma cases. The pathogenesis of Hodgkin lymphoma is unknown, but the Epstein-Barr Virus has been implicated.

Simply put, Non-Hodgkin lymphoma is any lymphoma lacking the morphological features of Hodgkin lymphoma, namely Reed-Sternberg cells and popcorn cells.² The majority of Non-Hodgkin lymphomas in children are aggressive and quickly growing. High-grade, aggressive tumors include Burkitt Lymphoma, Diffuse Large Cell Lymphoma, Anaplastic Large Cell Lymphomas and Lymphoblastic Lymphoma. Intermediate-grade Non-Hodgkin lymphomas are more common in adults than children and will not be discussed in this podcast.¹

Non-Hodgkin lymphoma can develop secondary to specific etiologies, including inherited and acquired immunodeficiencies, HIV, EBV, and certain genetic syndromes. Although in most cases, Non-Hodgkin lymphoma is not linked with an obvious etiology.

Epidemiology

Lymphoma is the third most common cancer in children fourteen years of age and younger, following acute leukemia and CNS tumours. Lymphoma accounts for 11% of childhood cancers in those aged 14 and younger.³

Lymphoma is the most common malignancy in adolescents, making up greater than twenty-five percent of cancer diagnoses in those aged fifteen to nineteen.³

Non-Hodgkin lymphoma is more common than Hodgkin lymphoma in children younger than fourteen, however incidence of Hodgkin and Non-Hodgkin are approximately equal if including all pediatric patients nineteen and younger.

Hodgkin lymphoma has a bimodal age distribution, wherein incidence peaks at age fifteen to thirty-five and again in adults aged fifty and older.¹ In early childhood, Hodgkin lymphoma is more common in boys than girls, with a male-to-female ratio of 5:1. However, by adolescence, the incidence is roughly equal between males and females. Hodgkin lymphoma is rare in children younger than 5 years old.

The peak incidence of Non-Hodgkin Lymphoma is seven to eleven years old and is more common in Caucasian patients than African American patients. Non-Hodgkin lymphoma is more common in boys than girls.

Overall survival of pediatric lymphoma is greater than ninety percent, making it one of the most curable pediatric cancers. It is, therefore, imperative that physicians (and medical students) maintain a high degree of clinical suspicion for the early signs of lymphoma and refer to pediatric oncology promptly.

Clinical Presentation

For both Hodgkin and Non-Hodgkin lymphoma, it is critical to ask about constitutional symptoms which include a fever greater than 38 degrees Celsius, weight loss of greater than ten percent total body weight over the course of six months and drenching night sweats. B symptoms are secondary to cytokine release by tumors. Please note, the absence of B symptoms does not rule out a cancer diagnosis.²

Hodgkin Lymphoma typically presents as painless, firm, enlarged lymph nodes in the cervical or supraclavicular regions.² It can also present as mediastinal lymphadenopathy. Mediastinal involvement can manifest as cough and dyspnea if the airway is compressed by a mediastinal lymph node, hoarseness if compression of the recurrent laryngeal nerve, superior vena cava syndrome if compression of the SVC or pleural effusion if the tumour has infiltrated the pleural space. Hepatosplenomegaly is another feature. Signs of bone marrow infiltration include anemia, neutropenia and thrombocytopenia. Another symptom could be cyclical fevers that come and go. Hodgkin lymphoma can also lead to nephrotic syndrome, specifically Minimal Change Disease.

The presentation of Non-Hodgkin lymphoma is more heterogeneous, where the signs and symptoms are dictated by specific subtype.² There may be painless, rapidly growing lymphadenopathy or signs and symptoms of mediastinal lymphadenopathy. As Non-Hodgkin lymphomas in children are faster growing tumors, children tend to present in later stages of the disease. Extranodal tissues such as the skin, bone, GI tract, bone marrow and CNS may be involved.

In North America, Burkitt lymphoma typically presents as an ileocecal abdominal mass and is described as sporadic Burkitt lymphoma.¹ This is in contrast to endemic Burkitt lymphoma, where the presentation is typically a jaw mass. To give a sense of the aggressive nature of this cancer, consider that it takes 5 days for a Burkitt tumor to double in size in contrast to 30 days for a Hodgkin lymphoma tumor.

Lymphoblastic Lymphoma typically presents as a symptomatic mediastinal mass, as described previously, and has a predilection to spread to the bone marrow and CNS.¹ Lymphoblastic Lymphomas typically derive from precursor T lymphocytes and, given spread to the bone marrow, may present similarly to Acute Lymphoblastic Leukemia (ALL). I refer the listener to the PedsCases podcast called Approach to Acute Leukemia in Children. As this can be diagnostically confusing, keep in mind that patients will be classified as Acute Lymphoblastic Leukemia with extramedullary disease if there are greater than twenty-five percent lymphoma cells in the bone marrow.

Diffuse Large B Cell Lymphoma usually presents as an abdominal or mediastinal mass. Anaplastic Large Cell Lymphoma can have skin involvement, dissemination to the liver, spleen, lung or mediastinum. Bone marrow and CNS are rarely involved with either of these subtypes.

Importantly, Non-Hodgkin lymphoma can present as an oncologic emergency.² Take time to commit to memory the following three manifestations of Non-Hodgkin lymphoma oncologic emergencies as they will require immediate, intensive care. Firstly, superior mediastinal syndrome is when a large mediastinal mass obstructs the airway or blood flow of the superior vena cava. This can present as dilated neck veins, asymmetrical facial swelling, or altered mental status. Secondly, CNS lymphomas manifesting as cranial nerve palsies, meningitis, or spinal cord compression. Spinal cord compression can present as acute paraplegia. Thirdly, tumor lysis syndrome is a severe metabolic derangement that occurs when a massive number of tumor cells lyse, releasing large amounts of potassium, phosphate and nucleic acids into the systemic circulation. The nucleic acids are metabolised into uric acid leading to hyperuricemia. Hyperkalemia is concerning as it can lead to the development of cardiac arrhythmias. Precipitation of uric acid in the renal tubules can lead to acute kidney injury. Superimposed calcium phosphate deposits in the renal tubules, resultant from hyperphosphatemia, adds to the development of an acute kidney injury. Without rapid intervention for tumor lysis syndrome, renal insufficiency, or even failure, as well as cardiac dysfunction can ensue. Take care to look for the signs and symptoms of these three categories of oncologic emergencies as these are the most frequent acutely life-threatening conditions of lymphoma in children.

Differential Diagnosis: Lymphadenopathy

The lymphadenopathy associated with Hodgkin lymphoma is painless, rubbery and without overlying inflammatory changes of the skin. These features, among others, can help you when evaluating the broad differential diagnosis of lymphadenopathy and deciding when to initiate workup for cancer in a child presenting with lymphadenopathy.

The differential diagnosis for lymphadenopathy includes infectious, autoimmune, lymphoproliferative and reactive disorders.⁵ In broad strokes, infectious etiologies would more commonly present as tender and mobile lymph nodes. A variety of viral infections, such as Epstein-Barr virus, cytomegalovirus and Human Immunodeficiency Virus (HIV), as well as bacterial etiologies such as tuberculosis, brucellosis and cat scratch disease can present with tender lymphadenopathy. Some etiologies may cause overlying skin changes, further distinguishing from a lymphoma presentation. An example of a parasitic cause would be toxoplasmosis. A fungal etiology could be histoplasmosis. Inflammatory causes include various collagen disorders, drug hypersensitivities, sarcoidosis, amyloidosis or serum sickness. I refer the listener to the PedsCases podcast titled “Approach to Lymphadenopathy” for an in depth look at the subject. Of note, non-lymph node etiologies of pediatric neck mass include a branchial neck cyst, which can become infected and increase in size rapidly.

Return to Case

After asking Peter and his mother some questions, you have determined that he does not display any constitutional symptoms. He has had a cough for the last month but has felt well. On physical exam, you note a unilateral, 2cm lymph node in the anterior cervical region of the neck. No other lymph nodes are palpated in other regions of the body and there is no hepato-splenomegaly. Auscultation of the lung fields are clear with equal entry bilaterally. All other components of the physical exam are unremarkable. You decide to order lab work and a CXR.

Investigations and Diagnosis

After collecting a detailed history, taking care to evaluate for infection and B symptoms among others, as well as a careful physical exam, we must decide how to proceed with investigations.

The goal of preliminary, non-invasive testing is to determine if a child needs a biopsy of their enlarged lymph node.² Even in a well-appearing child, it is appropriate to order laboratory and imaging studies if elements of the history and physical stand out as concerning to the physician. A complete blood cell count, electrolytes, Liver Function Tests (LFTs), serum lactate dehydrogenase, alkaline phosphatase, uric acid, blood urea nitrogen, creatinine, HIV serology and C-reactive protein levels is an appropriate initial panel. Consider EBV and CMV serology if there is bilateral involvement. We would consider a blood culture if a child is febrile. When in doubt, culture all pediatric patients with a fever.

Imaging options include chest radiography, lymph node ultrasonography and CT if clinical suspicion is high. A chest radiograph to assess for mediastinal involvement is a good first step and utilizes far less radiation than CT.

Children with chronic or generalized lymphadenopathy or with systemic symptoms should undergo lymph node biopsy without delay.² Specifically, if lymphadenopathy persists longer than six weeks or if there are noncontiguous, enlarged lymph nodes. Other concerning features would be any lymph node exceeding 2.5cm, limited mobility of lymph nodes, involvement of the left supraclavicular site, age greater than 10 years old or presence of B symptoms. Any of these features warrant a lymph node biopsy without delay. Specifically, an excisional lymph node biopsy is preferred over fine-needle aspiration or core-needle biopsy. The sample would undergo light microscopy as well as immunohistochemical and molecular studies to establish the diagnosis. Formal staging would follow to characterize the extent of disease and aid selection of the most appropriate therapy for the patient.

Treatment

Decisions regarding treatment of pediatric lymphomas are primarily based on the type of cancer and stage of the disease. Treatment is also said to be “risk adapted” meaning that it aims to minimize effects of treatment later in life without compromising the chance of cure. We will discuss the immediate and long-term complications of therapy in the following section.

In general, treatment consists of multiple chemotherapy drugs with or without radiation therapy. The rationale for multiple chemotherapy drugs is to have non-overlapping toxicities so that full doses can be administered for maximal efficacy. This approach to treatment is a significant contributor to pediatric lymphoma survival rates surpassing ninety percent. Combination chemotherapy has also led to a reduction in secondary cancers later in life.

The chemotherapy agents in the treatment of Hodgkin lymphoma are described by the mnemonic ABVD for earlier staged cancers, and the mnemonic BEACOPP for later

staged cancers. ABVD stands for Adriamycin (which is a brand name for doxorubicin), Bleomycin, Vinblastine, and Dacarbazine. BEACOPP stands for Bleomycin, Etoposide, Adriamycin (doxorubicin), Cyclophosphamide, Oncovin (vincristine), Procarbazine and Prednisone. Classical Hodgkin Lymphoma treatment can also include the monoclonal antibody Brentuximab vedotin. Similarly, Nodular Lymphocyte Predominant Hodgkin Lymphoma treatment can include the monoclonal antibody rituximab. Radiation is reserved for patients who did not demonstrate rapid response to the first few chemotherapy cycles and is given in such a way to minimize whole body exposure.

Treatment for Non-Hodgkin lymphoma is again multiagent systemic chemotherapy and/or immunotherapy with intrathecal chemotherapy. Radiation is only used if CNS involvement or superior mediastinal syndromes, or in refractory cases. Lymphoblastic lymphoma is treated using acute lymphocytic leukemia protocols which are entirely different from lymphoma protocols. The aggressive nature of Non-Hodgkin lymphoma lends itself to the risk of oncologic emergencies mentioned previously, all of which have specific treatment protocols.

Children with SVC syndrome should undergo emergent cytoreduction chemotherapy with prednisone or cyclophosphamide, or radiation therapy, to reduce the risk of severe cardiorespiratory morbidity. Patients with cranial nerve or spinal cord compression should undergo emergent chemotherapy or surgical decompression. Life-threatening tumor lysis syndrome must be treated with allopurinol and IV fluids with concomitant ECG monitoring. Further pharmacotherapy is required if serum potassium is greater than 6.5mEq/L and dialysis is required if the patient has reached kidney failure.

Review of Learning Points

We hope that you have gained the following learning points from this podcast:

1. Hodgkin and Non-Hodgkin Lymphoma are distinguished morphologically, and each further subdivide into various subtypes. All of which carry a unique presentation.
2. Lymphoma is the third leading childhood cancer.
3. Prognosis of pediatric lymphoma is excellent with prompt treatment.
4. Cervical lymphadenopathy is a common presentation in childhood lymphoma
5. Physicians and medical students should be aware of oncologic emergencies.
6. The principles of treatment are multi-agent chemotherapy with or without radiation.

References

1. Nelson's Textbook of Pediatrics, Chapter 523, by Goldman, S., Hochberg, J., and Cairo, M.

2. American Academy of Pediatrics' Journal *Pediatrics in Review* article entitled "Pediatric Lymphoma" by Ilia N. Buhtoiarov.
3. The Leukemia and Lymphoma Society of Canada Website provided the statistics of incidence and prognosis of pediatric lymphoma.
4. UpToDate article titled "Tumor lysis syndrome: Definition, pathogenesis, clinical manifestations, etiology and risk factors" by Richard Larson and Ching-Hon Pui provided information on tumor lysis syndrome.
5. Toronto Notes 2018, 34th edition, Section H12, Approach to Lymphadenopathy