

PedsCases Podcast Scripts

This is a text version of a podcast from PedsCases.com on "[Approach to Acute Leukemia in Children](#)." These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Approach to Acute Leukemia in Children

Developed by Amarjot Padda and Dr. Bev Wilson for PedsCases.com.
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Hi everyone! My name is Amarjot Padda and I'm a medical student at the University of Alberta. Today I will be discussing an approach to acute leukemia in children, more specifically focusing on Acute Lymphoblastic Leukemia or ALL. Before we get started, I would like to thank Dr. Bev Wilson, a Pediatric Oncologist at the Stollery Children's Hospital, for her help in developing this podcast.

Clinical Case:

Let's start with a clinical case! You are a medical student on your rural family medicine rotation. Your first appointment of the day is a new patient. Aiden a 5 year old boy brought in to the clinic today by his mother. She has been concerned about Aiden for the past few months. She has noticed that he has become increasingly tired. He no longer enjoys playing outside and his kindergarten teacher has noticed a decrease in his energy level. Aiden was taken to a local walk-in clinic twice in the last few months but each time was reassured that everything was okay. When you ask about any other symptoms, she mentions that she has noticed that Aiden has been limping for the last 2 weeks. On examination you notice some pallor, pale conjunctiva and a mild limp effecting his left leg. The rest of the examination is unremarkable. What is your impression of this case? As a primary care physician what are your next steps?

The objectives of this podcast are:

- Review epidemiology, etiology and pathogenesis of ALL
- Recognize the clinical presentation of ALL
- Review laboratory abnormalities which may indicate ALL
- Develop an approach to initial education, management and the referral process

Introduction:

According to the 2015 Canadian Cancer Statistics, leukemia represents a third of new cancer cases in children aged 0-14 years. Among the different types of acute leukemias, ALL is the most common pediatric cancer (2), and therefore will be the focus of this podcast. ALL is most commonly diagnosed in children from 3 to 5 years of age and is slightly more common in boys. Although ALL is curable in most cases, a diagnosis of ALL has a significant impact on the lives of children, and their families (2, 4).

Pathogenesis

Leukemia occurs as a result of a series of genetic mutations leading to aberrant hematopoiesis in the bone marrow. Let's quickly review normal hematopoiesis. Stem cells located in the bone marrow differentiate into either lymphoid or myeloid stem cells, forming two distinct lineages (5).

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The lymphoid lineage gives rise to lymphoblast cells that further differentiate into B lymphocytes, T lymphocytes and natural killer cells (5). The myeloid lineage gives rise to red blood cells, platelets, and myeloblastic cells. Myeloblast cells further differentiate into neutrophils, eosinophils and basophil cells (5). In children with ALL, this process is deregulated due to a series of genetic mutations, allowing clonal expansion of a single lymphoid progenitor cell or blast cell (1). The ability of this leukemic blast cells to proliferate and accumulate in the bone marrow essentially stops normal hematopoiesis or stops the normal bone marrow from working. Depending on the stage of hematopoiesis at which these mutations occurred, ALL could be further sub-categorized into B-cell ALL, T-cell ALL, and ALL of ambiguous lineage (5).

Etiology and Risk Factors:

The exact etiology of ALL has not been determined. Genetics likely play some role in the development and pathogenesis of leukemia as there is a higher incidence of leukemia in children with certain genetic conditions, including, Trisomy 21, Bloom syndrome, and Li-Fraumeni syndrome (1). While there may be an inherited genetic predisposition for some cases of leukemia, the majority are the result of somatic mutations or not related to inheritance (i.e. random events). There are no clearly identified environmental exposures that are linked to ALL other than radiation exposure. It is important to discuss this with parents, as many of them may feel guilt around their child's diagnosis.

Clinical Presentation:

The clinical presentation of ALL can vary significantly for each patient. A child with leukemia may present chronically with an array of non-specific symptoms to their family doctor or with more acute symptoms in an Emergency Department. Recently, more and more cases of childhood ALL are picked up incidentally on blood work often done for another reason. Let's go through some of the possible signs and symptoms of ALL as well as some lab abnormalities, which may increase your suspicion of ALL. The most common clinical presentation of ALL includes fever, fatigue and pallor (1). More generally, children with ALL tend to be irritable. Because these symptoms have a very broad differential diagnosis and ALL is very rare, ALL should not be the first diagnosis in mind when these patients present to primary care. However, it is important to follow-up with patients regarding these non-specific symptoms if they are persistent to ensure a diagnosis of ALL is not missed.

Blast cell proliferation in bone marrow can cause various hematological symptoms of leukemia including anemia, neutropenia and thrombocytopenia. The clinical features of the disease can depend of the degree of various cytopenias. Additionally, extra medullary invasion of the disease can result in CNS, or bone and joint involvement.

Let's first discuss the hematological symptoms of ALL. Common manifestations of anemia in ALL patients include pallor, fatigue, lethargy, and possible dyspnea (4). Parents will often describe how their child has a lack of energy, can no longer keep up with other kids, and no longer enjoys their usual activities. Neutropenia can present as recurring bacterial or invasive fungal infections, although this is a very rare presentation of ALL (1). Lastly, thrombocytopenia can present as a bleeding abnormality like bruising, petechiae, purpura, as well as mucosal bleeding (1). Infiltration of the lymphatic system is responsible for possible lymphadenopathy, hepatomegaly, and/or splenomegaly all of which can be presenting symptoms of childhood leukemia (1). In addition to the hematological symptoms of leukemia, there can be a wide variety of extra medullary symptoms. Of all the sites of extramedullary invasion, bone and joint involvement is relatively common. Up to 25% of patients present with bone or joint pain as the initial symptoms of concern (4). In addition to bone pain, children with bone and joint

involvement may present with a limp. ALL can also involve the Central Nervous System and boys can have testicular involvement. These will not be discussed in detail in this podcast. However, for these reasons it is important to do detailed neurological and testicular exams in addition the rest of the complete physical exam.

It is also important to note that ALL can present as an emergency in certain situations. Emergent complications related to ALL include febrile neutropenia, sepsis, hyperleukocytosis, superior vena cava syndrome or a mediastinal mass which can compress the trachea (5, 6).

Differential Diagnosis:

It is important to consider other more common causes of anemia, neutropenia and thrombocytopenia before ALL, as ALL is relatively rare. Systemic lupus erythematosus (SLE), Epstein- Barr virus (EBV) infections, parvovirus infections, as well as systemic juvenile idiopathic arthritis (JIA), can all present with a similar constellation of clinical findings and hematological abnormalities (5). Other malignancies, for example neuroblastoma can also have a similar presentation. In addition to these, aplastic anemia and other bone marrow failure syndromes can also present like ALL.

Let's go back to our case and discuss the presenting features of Aiden's illness. Aiden presented with many symptoms of anemia, including fatigue, lethargy, and pallor. Chronic anemia has a broad differential, including iron deficiency, folate deficiency, Vitamin B12 deficiency, renal disease, thalassemia, sickle cell disease, bone marrow suppression due to toxins or inflammation, as well as malignancies such as leukemia or lymphoma. In addition to the findings consistent with anemia, Aiden has recently developed a limp. What are your concerns? What investigations should you consider?

Investigations and Lab Abnormalities

Many new cases of ALL are being diagnosed based on blood-work done for another reason. Anemia, thrombocytopenia, and neutropenia are common findings on the CBC differential in ALL patients. It is important to note that the white blood cell count may be in the normal range or too high. In fact, it is most commonly within normal range in children with ALL (5). A peripheral smear is a reasonable next step if a primary care physician suspects ALL. While blasts on the peripheral smear may be diagnostic, ALL cannot be ruled out if there is an absence of blasts (6). In addition to a CBC with differential, a peripheral smear, a coagulation profile including PT, PTT, and fibrinogen can be ordered (6). If the patient is febrile, blood cultures should be considered (6). While these investigations can be ordered by a family physician, it is important that a child with suspected ALL be promptly referred to a pediatric oncologist for a full work-up. A definitive diagnosis can only be made by a pediatric oncologist following a bone marrow aspirate and biopsy.

Going back to our case, it would be reasonable to order a CBC and differential for Aiden. The results of the CBC would help you determine if Aiden is anemic, and also give you some clues about the underlying etiology.

The CBC and differential for Aiden showed that he had normocytic anemia, thrombocytopenia, a mild leukopenia, neutropenia as well as the presence of blast cells. A decrease in all cell lines, as in Aiden's case, can be described as pancytopenia. Based on these findings, a peripheral smear was also ordered. The peripheral smear showed an increase in blast cells.

Approach to initial management and referral

If a primary care physician suspects ALL, the child should promptly be referred to a pediatric oncologist for urgent assessment and management.

Leukemia, or any other cancer, can be a very difficult diagnosis for parents, siblings and of course the affected child. Communication with the family, and the patient, is a key component of care for leukemia patients. Some tips for medical students and physicians working in primary care include, not giving bad news over the phone, ensuring you are equipped with information regarding the referral process, discuss what to expect during the initial work-up and ensuring that you have set aside enough time to have a meaningful discussion with the family. It is also important to note that without a bone marrow biopsy and aspirate, the diagnosis is not clear. Therefore, referring primary care physicians need to be careful about giving the patients an exact diagnosis as this should be left for the pediatric oncology team. It is important that all members of the health care team are giving the same information to the family to reduce confusion and maintain trust. All major tertiary centers across Canada have a pediatric oncology ward. However, if a family is from a smaller town they may have to travel to the appropriate center to receive care.

Depending on the age of the child, communicating the diagnosis with the child can be difficult. The type of discussion with the child depends on the age of the child, as well as their developmental level. For example, a teenager is generally given the option of taking part in all discussions regarding the diagnosis, and management of their condition. Whether the child is a part of the diagnostic meeting or not, you need to let the child know what to expect in the short and long term. One way to communicate a diagnosis of leukemia to a younger child is to tell them that they have a problem in their blood. For the health care team, it is important to develop trust with the child. Part of building rapport with children means not lying to them about the length of admission and treatment, including possible painful procedures. Being honest with children about what to expect in the short term is very important to help them cope with the hospital experience. In addition, you need to talk to the child about what is important to them, including missing school, sports, playing with their friends etc. Most pediatric oncology teams have access to child life therapists to help pass information on to children.

Treatment and Prognosis

Leukemia is treated with chemotherapy. Various factors including cytogenetic testing are used to risk stratify the patients which is used to tailor the treatment protocol. With ALL, all patients will get CNS prophylaxis (chemotherapy into the spinal fluid) even if they do not present with CNS disease. We will not be discussing the treatment for leukemia in detail in this podcast. It is important to note that chemotherapy for leukemia is likely to continue over 2-3 years therefore patients and families need to be educated accordingly (4).

With modern therapies there is an 85-90% cure rate in children with standard risk B cell leukemia (2, 4). Long term sequelae depend on the treatment protocol used but can include neurocognitive defects, osteonecrosis, cardiotoxicity, infertility and secondary neoplasms (5).

Conclusion

Let's review some of the important concepts we covered in this podcast:

- Leukemia occurs as a result of a series of genetic mutations leading to aberrant hematopoiesis in the bone marrow
- A child with leukemia generally presents with an array of non-specific symptoms including fever, fatigue and pallor. In patients presenting with these non-specific

symptoms, ALL should not be at the top of your differential as it is very rare. However, persistent symptoms should be followed up in primary care.

- Anemia, neutropenia and thrombocytopenia are common manifestations of leukemia.
- If a primary care physician suspects ALL, the child should promptly be referred to a pediatric oncologist for urgent assessment and management

Let's re-visit our case once again. Based on the findings on the CBC and peripheral smear, as the rural family physician you urgently refer Aiden to the pediatric oncology team at the Stollery Children's Hospital in Edmonton. You also discuss the process of referral with Aiden's family and answer their questions to the best of your ability. You inform the family of the various support groups available in the community. You also mention that the multidisciplinary oncology team in Edmonton has a social worker that can help make arrangements for their stay in Edmonton. Aiden is seen by the pediatric oncology team at the Stollery. A full work-up is done—Aiden is diagnosed with ALL and chemotherapy is initiated promptly. You continue to follow Aiden as a general practitioner in the community.

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