https://doi.org/10.33591/sfp.46.7.up1

ACUTE LYMPHOBLASTIC LEUKAEMIA IN A 7-YEAR-OLD PRESENTING WITH LOWER LIMB PAIN – NOT JUST YOUR SIMPLE GROWING PAINS!

Dr Lin Xin, Dr Jeffrey Jiang Song' En

ABSTRACT

This is a case report of a 7-year-old boy who presented with lower limb pain. He was initially presumed to have growing pains but was subsequently diagnosed with acute lymphoblastic leukaemia (ALL). This case highlights the important clinical presentations and differential diagnoses of ALL that a family physician should be cognizant about to avoid misdiagnosis. It also demonstrates the importance of understanding the patient and family's perspectives when evaluating a child with lower limb pain. This enables us to anticipate and meet their needs.

Keywords: Lower limb pain, growing pains, acute lymphoblastic leukaemia

SFP2020; 46(7): 32-35

INTRODUCTION

This is a 7-year-old boy who had multiple visits to various primary care providers and was diagnosed to have "growing pains". He subsequently presented to the Children's Emergency department for persistent lower limb pain and was subsequently diagnosed with ALL. ALL accounts for up to a quarter of all childhood cancers. Musculoskeletal pain is a presenting complaint of ALL in up to 43 percent of patients.[1] Hence it is important for family physicians to have a high index of suspicion and actively look out for relevant signs and symptoms.

PATIENT'S REVELATION

The patient had no past medical history, and presented to the Children's Emergency in July 2018 with a four-month history of left lower limb pain – mainly over his thigh and calf. The pain was initially intermittent and brought on by activities such as running, jumping, and Taekwondo. Subsequently, the pain became persistent at rest and had been awakening the child from sleep over the past month prior to presentation. There was no associated trauma to the area before the onset of pain. He had visited various primary care providers several times, and the diagnosis of growing pains was made. He last visited the polyclinic in June 2018 with similar complaints. He was noted to be thin, but this was attributed to being constitutional. The full range of movement and power of his lower limbs was documented, but there was no mention of lymphadenopathy or abdominal masses. Hence, he was treated symptomatically for his pain.

At the initial encounter, his parents appeared concerned and questioned: "Why is my child's pain not getting better despite the medications?"

On further history, several "red flags" were elicited. He had one week of fever above 38-degree Celsius with no localising infective symptoms. He also had abdominal bloating and decreased appetite associated with five percent weight loss (17.2kg to 16.2kg) over the past month. He had no family history of malignancy or autoimmune diseases. There was also no recent travel or tuberculosis contact.

On physical examination, he had a temperature of 38.6-degree Celsius, heart rate - 136 beats per minute, blood pressure - 119/63mmHg and oxygen saturations of 100 percent on room air. He had an antalgic gait, appeared cachectic and had abdominal distension. On palpation, he had hepatosplenomegaly with multiple cervical, epitrochlear and inguinal lymphadenopathy. There was no testicular enlargement or tenderness. On examination of his peripheries, there was no evidence of a rash, joint inflammation, or muscle tenderness.

Preliminary diagnosis at this point was that of malignancy with differential diagnoses of infection and autoimmune disease. The need for further inpatient evaluation was explained to the child and his parents who appeared shaken asked: "Is my child's condition serious?"

INPATIENT PROGRESS

X-ray of his lower limb did not reveal any structural abnormalities. His full blood count (FBC) revealed leucocytosis (white blood cells (WBC) 11.52x10^9/L) and bicytopenia (haemoglobin of 9.7g/dL, platelets 142x10^9/L). Peripheral blood film (PBF) showed five percent blasts. LDH was high at 4937U/L. Renal and liver panel returned normal. Bone marrow aspirate (BMA) and trephine showed 51 percent lymphoblast and karyotyping revealed t(1;19) translocation. The evaluation was consistent with the diagnosis of ALL. A family conference was held during which, the diagnosis and management plans were shared with the family.

TREATMENT AND RESPONSE

In view of his age group, WBC count and t(1:19) translocation with no unfavourable cytogenetics, the patient was considered

LIN XIN
Family Medicine Resident,
Department of Family Medicine,
National University Health Systems, Singapore

JEFFREY JIANG SONG' EN
Registrar, St Luke's Hospital, Singapore

in the low-risk group under the National Cancer Institute (NCI) grading. He was later reclassified as high risk given positive minimal residual disease (MRD) after induction treatment, which suggests remaining leukemic cells in the patient. He was escalated from a standard risk to a high-risk Malaysia-Singapore Acute Lymphoblastic Leukaemia (MASPORE) chemotherapy protocol and subsequently underwent CAR-T immunotherapy in April 2019. He is currently in remission and has been participating in activities such as cycling and is planned to return to school this year.

GAINING INSIGHT

In managing the patient, the following questions arose:
1. What are the clinical features of ALL?
2. What are growing pains, and what are the red flags for a child complaining of lower limb pain?
3. How can family physicians appreciate the patient's perspectives and address concerns of both parents and child when dealing with childhood cancers?

STUDY THE MANAGEMENT: HOW DO WE APPLY INSIGHTS OF THIS PATIENT INTO OUR PRACTICE AS FAMILY PHYSICIANS?

Understanding the presentation of acute lymphoblastic leukaemia

ALL is a haematological malignancy where there is an overproduction of immature leukocytes by the bone marrow. It is the most common childhood cancer in the world, with peak occurrence between the ages of 2 to 5 years old. A meta-analysis that included more than 3000 children from 33 studies showed that the most common presentations of ALL are: hepatomegaly (64 percent), splenomegaly (61 percent), lymphadenopathy (50 percent), fever (50 percent) and musculoskeletal pain (43 percent).[1,2] Other less common presentations include headache, testicular enlargement, and symptoms arising from a mediastinal mass. FBC often shows leucocytosis, anaemia and thrombocytopenia. Blast cells may be present on PBF. Confirmatory investigations include BMA, cytogenetics, and karyotyping.

Causes of leg pain in a child – growing pains and other differential diagnoses

Growing pains also termed "idiopathic nocturnal pains of childhood" is a common and benign condition that resolves spontaneously within 1 to 2 years. There is no consensus or definition but is often used to describe the pain that wakes the patient up at night. The features are summarised in Table 1. Growing pains are the most common explanation of lower limb pain with prevalence up to 37 percent in school-going children.[3] In a retrospective study of 148 children diagnosed with haematological malignancy between March 2002 to February 2007 in Singapore, 14.2 percent presented with bony complaints and 71.4 percent were misdiagnosed at the initial visit. It took a median of 21 days to arrive at the correct diagnosis, resulting in delayed treatment.[12] One should be conscientious when faced with recurrent bony complaints and do a thorough history and physical examination, eliciting red flags that may prompt early referral and evaluation of aetiologies mentioned in Table 2.

Table 1: Features of growing pains[4]

Features of growing pains

• Typical age of presentation: 3 to 12 years.
  ○ Location of pain: Primarily lower extremities. Often bilateral in thigh, calf, popliteal fossa or shin.
• Character of pain:
  ○ Paroxysmal and can be severe.
  ○ Occurs in the evening or night-time and may interrupt sleep.
  ○ Rarely limits usual activities.
  ○ Duration of pain is usually episodic and may last for at least three months to years.
• Pain is often relieved by massage and first-line analgesia such as paracetamol and ibuprofen.
• Pain may be associated with headaches and abdominal pain.
• Physical examination is normal.
• Ancillary tests if performed are normal.

Table 2: Red flags that may suggest other aetiologies

Red flags	Possible aetiologies
History	
Trauma	• Fractures • Overuse injuries
Progressive and persistent pain Activity limitation Fever, malaise Loss of weight	• Malignancies such as bone tumours and leukaemia • Infection
Physical examination	
Pallor, Bruising, Hepatosplenomegaly Splenomegaly Lymphadenopathy Testicular enlargement	• Leukaemia (Suggestive of two cell lines involvement) • Leukaemia or malignancy – increased mitosis
Palpable mass	• Bone tumours
Localised features of inflammation - Point tenderness - Erythema - Warmth	• Infection • Myositis
Hip pain, Trendelenburg gait	• Perthes disease • Developmental Dysplasia of the hip (DDH) • Osteonecrosis of the hip • Slipped Capital Femoral Epiphysis (SCFE)
Frontal bossing Widening of wrist Lateral bowing of femur and tibia	• Rickets
Joint involvement Systemic features	• Systemic Lupus Erythematosus (SLE) • Henoch Schoenlein Purpura (HSP) • Dermatomyositis • Juvenile Idiopathy Arthritis (JIA)

Concerns and perspectives

Child
This is a previously well child. Since the onset of his lower limb pain four months ago, he had to forgo his favourite activities such as Taekwondo. The evaluation and treatment process included painful procedures, such as BMA and intrathecal medications. He also had recurrent admissions for treatment and complications such as neutropenic fever for which he was treated with intravenous antibiotics and recovered.

A diagnosis of cancer significantly disrupts a child's life. Furthermore, many children may not fully comprehend the meaning of cancer at a very young age. In a qualitative study supported by Korea Leukaemia Childhood Foundation, it was noted that childhood cancer survivors tend to question why they were inflicted with cancer. These cancer survivors tend to cite internal causes such as being 'bad children', unhealthy eating habits and stress-prone personality. Without knowledge and understanding of their condition, this may result in unnecessary self-reproach.[5]

Children often had to be taken out of school during the period of intensive treatment, and there is often a negative impact on their education and employment when they enter adulthood.[6]

Survivors of childhood cancer also experience the stress of relapse, development of secondary cancers and complications of treatment.[7]

Parents
The patient's parents felt anxious and helpless about the persistent pain he had. The diagnosis and treatment of childhood cancer is a significant source of stress for the parents, with the peak being the diagnosis and at relapse.[8] Cancer treatment is often costly and can pose financial burdens, putting further strain to the couple's relationship.[7] Childhood cancers often cause parents to be overprotective and emotional even after achieving remission[9], affecting the parent-child relationship in a long run.[8]

DISCUSSION AND CONCLUSION

Musculoskeletal pain in the paediatric population is a common complaint seen in primary care. It is essential for family physicians to be vigilant and systemically to evaluate each child with a thorough history taking and physical examination. ALL and growing pains may present similarly with musculoskeletal pain. However, they have salient differences, as presented in this case and have a vastly different disease trajectory. One can consider simple laboratory investigations such as FBC and early referral for patients with red flags.

Childhood cancer is a stressful event for both the children and their parents. Family physicians may encounter these patients at initial presentation, during treatment, or in remission. Organisations with resources available to support such individuals include the Children's Cancer Foundation, Children's Society and Club Rainbow.

After remission, patients tend to return to their primary care physicians for health maintenance and acute illnesses. Vaccination is an important aspect that primary care physicians can follow-up with as most children do not maintain protective titres for vaccine-preventable diseases following cancer therapy. Several studies have shown that a universal one dose schedule of revaccination is beneficial.[10,11] Influenza vaccinations are also recommended for patients and their families.

It is also important to be vigilant about signs and symptoms of relapse, which often have similar symptomology to the initial presentation. As relapse commonly occurs in the bone marrow, persistent suppression of any cell line for more than a month or suppression of two cell lines requires prompt referral back to the tertiary centre. Every patient's condition differs, and family physicians may need guidance to manage them. Moving forward, we can consider a collaboration between the restructured hospital and primary care via a cancer survivorship program, which is still at an infancy stage in Singapore.[13] This provides a template for the patient's primary oncologist to provide important information on patient's condition necessary for seamless transfer of care – including signs and symptoms at presentation, treatment received, frequency, and mode of surveillance. Primary care physicians play a strategic role in providing holistic care for paediatric patients – from making an accurate diagnosis to active surveillance and preventive care.

REFERENCES

1. Clarke RT, Van den Bruel A, Bankhead C, Mitchell CD, Phillips B, Thompson MJ. Clinical presentation of childhood leukaemia: a systematic review and meta-analysis. Archives of disease in childhood. 2016 Oct 1;101(10):894-901.
2. Philip A. Pizzo, David G. Poplack. Principles and Practice of Pediatric Oncology 4th Edition [Internet]. United States of America: Lippincott Williams & Wilkins Publishers; 2001 [updated 2001 November; cited 2020 August 20]. Available from: http://ndl.ethernet.edu.et/handle/123456789/13193
3. Evans AM, Scutter SD. Prevalence of "growing pains" in young children. The Journal of pediatrics. 2004 August 1;145(2):255-8.
4. Naish JM, Apley J. 'Growing pains': a clinical study of non-arthritic limb pains in children. Archives of disease in Childhood. 1951 Apr;26(126):134.
5. Yi J, Kim MA, Parsons BG, Wu YP. Why did I get cancer? Perceptions of childhood cancer survivors in Korea. Social work in health care. 2018 April 21;57(4):300-14.
6. Maule M, Zugna D, Migliore E, Alessi D, Merletti F, Onorati R, Zengarini N, Costa G, Spadea T. Surviving a childhood cancer: impact on education and employment. European Journal of Cancer Prevention. 2017 July 1;26(4):351-6.
7. Nipp RD, Kirchhoff AC, Fair D, Rabin J, Hyland KA, Kuhlthau K, Perez GK, Robison LL, Armstrong GT, Nathan PC, Oeffinger KC. Financial burden in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Journal of clinical oncology. 2017 October 20;35(30):3474.
8. Wiener L, Battles H, Zadeh S, Pelletier W, Arruda-Colli MN, Muriel AC. The perceived influence of childhood cancer on the parents' relationship. Psycho-oncology. 2017 Dec;26(12):2109-17.
9. Long KA, Keeley L, Reiter-Purtill J, Vannatta K, Gerhardt CA, Noll RB. Child-rearing in the context of childhood cancer: Perspectives of parents and professionals. Pediatric Blood & Cancer. 2014 Feb;61(2):326-32.
10. Fayea NY, Fouda AE, Kandil SM. Immunisation status in childhood cancer survivors: A hidden risk which could be prevented. Pediatrics &

Neonatology. 2017 December 1;58(6):541-5.
11. Han JH, Harmoney KM, Dokmeci E, Torrez J, Chavez CM, Cordova de Ortega L, Kuttesch JF, Muller M, Winter SS. Dynamic re-immunisation of off-treatment childhood cancer survivors: An implementation feasibility study. Plos one. 2018 Feb 1;13(2):e0191804.
12. Teo WY, Chan MY, Ng KC, Tan AM. Bony presentations of childhood haematological malignancy to the emergency room. Journal of Paediatrics and Child Health. 2012 Apr;48(4):311-6.
13. Loh KW, Ng T, Choo SP, Saw HM, Mahendran R, Tan C, Chang GC, Ong YJ, Yee AC, Chan A, Soo KC. Cancer supportive and survivorship care in Singapore: current challenges and future outlook. Journal of global oncology. 2018 Feb;4(1):1-8.