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Bilateral Nephromegaly And Bone Swelling As An Initial Presentation Of Acute Lymphoblastic Leukemia - A Case Report.

Dr. Mahesh Mamilla
Department of Internal Medicine
Sri Venkateswara Medical College
Dr. Vaishnavi Sabesan
Department of Internal Medicine.
Government Kilpauk Medical College and Hospital.
Dr. Deipthan Prabakar
Department of Internal Medicine.
Government Kilpauk Medical College and Hospital.
Dr.Samhitha Gundakaram
Department of Internal Medicine.
Dr. YSR University of Health Sciences
Dr. Pallavi Ladda
Department of Medical Oncology.
Basavatharakam Indo American hospital and Research Institute

Abstract:
Background:
Acute lymphoblastic leukemia is a malignant and aggressive disease of the bone marrow characterized by uncontrolled growth of early lymphoid precursor cells, which gradually replace the normal cells that make up the hematopoietic system in the marrow. ALL is the most common type of cancer in children. Bilateral Nephromegaly and swelling of the cheekbone is a rare initial presentation of ALL
Case Presentation:
We describe a 13-year-old female patient referred to our hospital for progressive swelling of the left cheek for 2 months and decreased serum calcium and vit D3 levels. On examination, she was afebrile, pale, not icteric. Her vital signs and respiratory and abdominal examinations were unremarkable. Her examination revealed no lymph node enlargement and no hepatosplenomegaly. Her height and weight were below the 10th percentile. Her blood workup revealed microcytic hypochromic anemia, thrombocytopenia, mild leukocytosis with basophilia with no blasts, increased CRP, LDH levels, increased serum protein, and phosphorus levels, Chest X-ray was normal. USG abdomen revealed b/l enlarged kidneys with heterogeneous texture. The patient's age, BMI, history of progressive bone swelling, CBC findings (mild leukocytosis with basophilia, anemia, and thrombocytopenia), and bilateral kidney enlargement prompted us to think of hematological malignancies. Bone marrow aspiration was performed which revealed 94% blast cells and Immunophenotyping showed positive CD10, CD19, CD22, CD79a, CD34, and CD45 thus confirming the diagnosis of B- Acute Lymphoblastic Leukemia.
Conclusion:
The initial absence of blasts in the peripheral smear, along with the lack of lymphadenopathy and hepatosplenomegaly, can pose a significant diagnostic challenge in pediatric patients suspected of having leukemia. As early diagnosis and treatment are crucial for achieving a favorable prognosis, it is essential to maintain a high index of clinical suspicion when evaluating pediatric patients presenting with bone pain and bilateral nephromegaly for leukemia.

Keywords: *Renal, bone, leukemia*

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I. Background

In clinical practice, we see a lot of pediatric patients coming to the outpatient department with nonspecific bone pain. Growing pain is a common condition among children. It is a common practice to rule out

leukemia based on blood cell counts, blasts in peripheral smears, and hepatosplenomegaly. However, the initial presentation of ALL is variable, and ruling out leukemia based on these might turn out to be wrong. Early diagnosis is critical for prognosis and survival in these patients. Here is one such case report.

II. Case presentation

A 13-year-old female patient was referred to our hospital for swelling of the cheek and decreased calcium (8 mg/dL), and reduced vit D3 level (11.8 ng/mL (ref:30-100 ng/mL)). The patient was previously diagnosed with chronic sinusitis and had septoplasty + FESS + B/L SMR. She reported increased swelling of the left cheek for the past 2 months. Upon general examination, the patient was afebrile, pale, not icteric, pulse= 90/minute, BP= 100/70 mm Hg. Height and Weight were below the 10th percentile (Figure no 1). Respiratory and abdominal examinations were unremarkable. The cheek swelling was hard in consistency (Figure no 2). No neurocutaneous findings, Sexual Maturity Rating- A2B4P4

Secondary hyperparathyroidism was suspected, and lab investigations were ordered.

Figure no 1: Growth chart

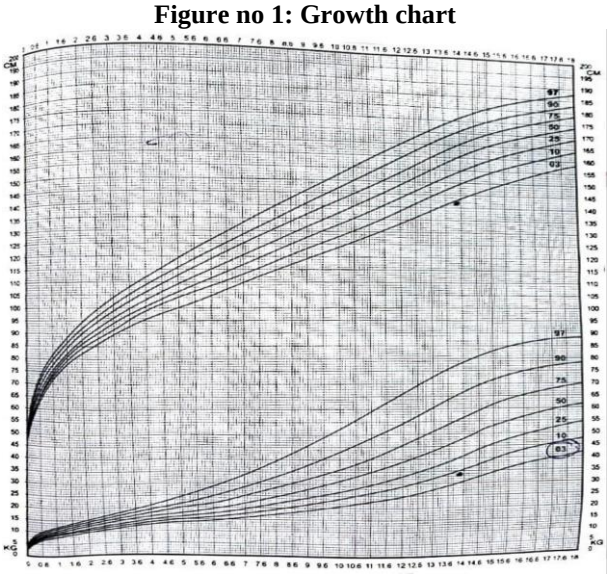

Figure no 2: Cheekbone swelling

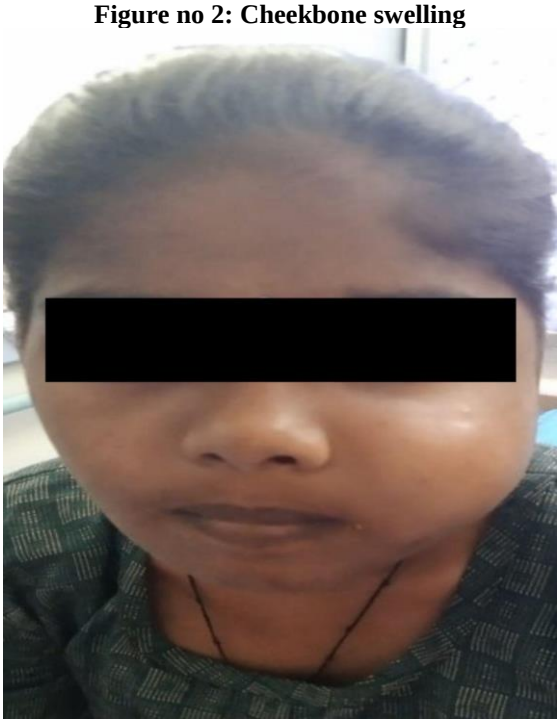

Table no 1: Complete blood count

	27/01/2023	04/02/2023	05/02/2023
Hemoglobin	9.4 g/dl	7.3 g/dl	7.4 g/dl
RBC	4.23 million/mm3	3.25	3.29
HCT	30.3%	24%	24%
MCV	71.6 fL		
MCHC	31.0 g/dl		
RDW-SD	60.2 fL		
RDW-CV	25.2%		
WBC	12,000 cells/mm3	2,400 cells/mm3	1080 cells/mm3
Neutrophils	5.2%	16%	16%
Lymphocytes	82.8%	16%	08%
Monocytes	11.5%	01%	01%
Eosinophils	0.1%		
Basophils	0.4%		
Platelet count	68,000 cells/mm3	55,000 cells/mm3	70,000 cells/mm3
Peripheral smear	RBC- anisocytosis, microcytic, hypochromic WBC- leukocytosis, no blasts PLT- reduced	No blasts	No blasts

Table no 2: Renal function test

Random blood sugar	124 mg/dl
Urea	22 mg/dl
Creatinine	0.85 mg/dl
Sodium	140 mEq/L
Potassium	5.6 mEq/L (3.5-5.10 mEq/L)
Chloride	103 mEq/L

Table no 3: Liver function test

Serum bilirubin Direct Indirect	0.9 mg/dl 0.3 mg/dl 0.6 mg/dl
SGOT	45 U/L
SGPT	55 U/L
Serum ALP	120 U/L
Total protein	5.5 g/dl
Albumin	3.0 g/dl
Globulin	2.5 g/dl

Table no 4: Bone metabolism assessment

Calcium	10 mg/dl
PTH	33.3 pg/mL (12.0-88 pg/mL)
25-OH vit D3	21.69 ng/mL (30-100 ng/mL)
phosphorous	8 mg/dL (2.5-4.5 mg/dL)
T3	0.83 ng/mL
T4	11.5 mcg/dL
TSH	2.72 mIU/L

Table no 5: Other investigations

CRP	48 mg/L (less than 6 mg/L)
LDH	1100 IU/L
cholesterol	234 mg/dL
triglyceride	304 mg/dL
Serum Uric Acid	5.4 mg/dL (2.5-6.2 mg/dL)

Table no 6: Urine tests

Protein	38.5 mg/dL (0-8 mg/dL)
Creatinine	57.7 mg/dL (16-327 mg/dL)
PCR	0.67 (0.075 -0.15)

Table no 7: USG abdomen

Liver	Normal size and texture
Spleen	Normal size and texture
Gallbladder	Distended
Pancreas	Normal
Urinary bladder	Distended
Kidney	R- 12.5X6.2 cm, L-12X5.5 cm, bilaterally enlarged kidneys, altered and heterogenous echotexture No evidence of free fluid

Table no 8: Bone Marrow Aspiration

- Hypercellular
- Trilineage hematopoiesis decreased
- DIFFERENTIALS

1. Blasts:94%
2. Neutrophils:01%
3. Lymphocytes: 03%
4. Erythroid:02%

Table no 9: Other investigations

CSF cytology	No evidence of malignancy
Echo	Normal
Chest Xray	Normal
Blood C/S	No growth

Even though the patient's peripheral smear showed no evidence of blast cells (Table no 1), the patient's age, BMI, history of progressive bone swelling, CBC findings (mild leukocytosis with basophilia, anemia, and thrombocytopenia) (Table no 1), and bilateral kidney enlargement in the ultrasound (Table no 7) prompted us to think of hematological malignancies. Bone marrow aspiration was performed which showed 94% blast cells (Table no 8) and a hematologist's opinion was sought. Immunophenotyping showed positive CD10, CD19, CD22, CD79a, CD34, and CD45 thus confirming the diagnosis of B- Acute Lymphoblastic Leukemia. Serum levels of uric acid, potassium, phosphorus, and lactate dehydrogenase (LDH) were checked to determine the level of tumor lysis (Table no 2, Table no 4, Table no 5). Serum LDH and serum phosphorus were elevated. Chest x-ray was negative for mediastinal mass, the blood culture showed no organism growth and CSF cytology was negative for malignant cells (Table no 9). Before administering anthracycline, baseline Echocardiography was done (Table no 9). The patient was started on the Modified BFM ALL-95 protocol and she achieved complete remission. Unfortunately, the patient died of sepsis during the consolidation phase.

III. Discussion and Conclusion

ALL accounts for approximately one-third of all childhood malignancies and is the most common form of cancer in children. The distribution of ALL categories is B lineage (85 percent), T lineage (10 to 15 percent), and NK lineage (<1 percent). The incidence of childhood leukemia appears to be increasing. The estimated incidence increased from 25 cases per million in 1975 to 41 cases per million in 2015 [1].

The presentation of ALL in children is variable and presents a diagnostic dilemma. In a meta-analysis that included 33 studies and a total of 3,084 children with leukemia, the results indicated that the most frequently reported symptoms were hepatomegaly and splenomegaly, which were observed in 64% and 61% of the cases, respectively. Other common symptoms reported included pallor (54%), fever (53%), bruising (52%), recurrent infections (49%), fatigue (46%), back pain (43%), hepatosplenomegaly (42%), lymphadenopathy (41%), bleeding tendency (38%), and rash (35%).[2]. The white blood cell (WBC) count may be low, normal, or high at the time of presentation.

Musculoskeletal pain is a common presenting symptom in ALL. Maman et al, reported that out of the 765 children with leukemia evaluated, 240 reported musculoskeletal symptoms, such as bone pain, arthralgia, low back pain, limping, arthritis, and refusal to walk (31.4 %) [3]. However, the skull has been an uncommon site of

involvement, and if involved, it is often confused with endocrine disorders, osteopetrosis, and extramedullary hematopoiesis secondary to hemolytic anemias. Recognizing the distinctive features of leukemia in imaging studies such as X-rays, CT scans, and MRI scans can facilitate early identification and prompt intervention. Regarding its pathogenesis, the disease itself is responsible for the direct or indirect activation of osteoclasts through the production of mediators by lymphoblasts [4]. Therefore, the activation of osteoclasts by lymphoblasts could be responsible for releasing bone phosphate which results in higher serum phosphate values in this patient. Studies show that childhood leukemia with musculoskeletal involvement had the characteristics of minimal or absent hematologic abnormalities and peripheral blast counts as seen in this patient [5].

Leukemic infiltration is most frequently seen in bone marrow, spleen, lymph nodes, and liver [6]. Extramedullary involvement of the kidneys is uncommon during the initial presentation. The frequency of nephromegaly in ALL patients has been reported to be between 2% and 24% [7]. Although renal involvement in ALL is occasionally seen, renal insufficiency is reported to occur in less than 1% of cases [8]. Kidney infiltration in ALL is usually asymptomatic and detected by the presence of a palpable abdominal mass or imaging. In renal ultrasound, leukemic infiltration may be suspected by the presence of enlarged kidneys with a hyperechogenic pattern/ the presence of hypoechogenic nodular lesions in the kidney cortex/ loss of corticomedullary differentiation [7]. When renal infiltration occurs, it can be associated with the involvement of other organs such as the central nervous system, testicles, and skin [7]. Therefore, other investigations are necessary to rule out the involvement of such organs. In the majority of cases that have been reported, there is a noticeable improvement in renal size following the commencement of acute lymphoblastic leukemia (ALL) treatment. Therefore, recurrence of kidney enlargement suggests relapse of ALL.

Diagnosing leukemia in a patient with marked leukocytosis can be easy. However, it is crucial to bear in mind that almost 50% of children with ALL may present with leukocyte counts lower than 11,000 on their initial CBC. As a result, it is important to acknowledge that leukemia can present with a broad range of white blood cell counts on the initial CBC [9]. Several factors could contribute to the underreporting of blasts on a CBC in cases of leukemia. These factors may include the limited experience of the individual interpreting the smear, uncertainty in identifying blasts due to similarities with activated lymphocytes in children, reduced numbers of blasts in cases with low leukocyte counts, or blasts not circulating in the blood. Even if no blasts are identified on the CBC, it is important not to rule out a diagnosis of acute lymphoblastic leukemia (ALL).

Studies show that in children with less than 50,000 leukocytes at diagnosis and without other adverse prognostic factors, a cure rate of up to 80% can be achieved. In a group of patients with more than 50,000 leukocytes at diagnosis, the chances of being cured would be reduced to 50% [9]. Early diagnosis is life-saving in ALL. Apart from the pallor and cheekbone swelling, our patient had none of the typical symptoms. Therefore, thorough clinical assessment, vigilant screening of the cell counts (especially basophils), and bone marrow aspiration play a vital role in diagnosing pediatric patients with unexplained pallor, bone symptoms, and bilateral renal enlargement.

The impact of renal leukemic infiltration and musculoskeletal involvement on the prognosis and survival of children with ALL is uncertain. Extensive research should be carried out to aid us in attaining a more holistic understanding of the atypical presentations of Acute Lymphoblastic Leukemia in children, their impact on prognosis, and for a better design of improvised therapeutic regimens in the future.

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