Orthopedic manifestation as the presenting symptom of acute lymphoblastic leukemia

Amrath Raj B K^a, Kumar Amerendra Singh^b, Hitesh Shah^{a,*}

^a Department of Orthopaedics, Kasturba Hospital, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India

^b Department of Orthopaedics, Manipal Academy of Higher Education, Manipal, India

ARTICLE INFO

Keywords:

Childhood leukemia
Acute lymphoblastic leukemia
Bone pain
Orthopedic manifestation

ABSTRACT

Introduction: The diagnosis of Acute lymphoblastic leukemia (ALL) is delayed due to vague presentation and normal hematological investigations.

Objective: The objectives were to identify the frequency of ALL cases presented to the orthopedic department and with normal hematological investigations.

Material and methods: 250 consecutive ALL cases were retrospectively evaluated to identify cases with musculoskeletal manifestations, and laboratory investigations.

Results: Twenty-two patients (4- vertebral compression fractures, 12- joint pain, 6- bone pain), presented primarily to the orthopedic department. Six patients had a normal peripheral smear.

Conclusion: The primary physician should maintain a high index of suspicion despite a normal peripheral smear.

1. Introduction

Leukemia is the most common form of childhood cancer and may virtually affect any organ system.^{1,2} The disease is always disseminated at the time of diagnosis, and the diagnosis is often obscure when the patient is first seen.² The variable frequency of musculoskeletal manifestations in acute lymphoblastic leukemia reported in the literature ranges from 21% to 59%, and sometimes the orthopedic surgeon is the primary physician.^{1–5} Often, the skeleton is the first body system to demonstrate overt manifestations of the acute form of the disease.¹ Besides, the correct diagnosis may be delayed, as evaluation may be wrongly focused on a presumed rheumatic disease or other simulating diseases like osteomyelitis, septic arthritis, Perthes' disease, sickle cell disease.^{1,6–8}

The peripheral blood count and smear may be normal in patients with orthopedic manifestations, especially in leukemia of childhood.^{1,4,6,8} At initial presentation, many patients have non-specific signs and symptoms as well as lab diagnosis. Very little has been written about leukemic involvement of the spine. Generalized osteoporosis and vertebral compression fractures are less frequent manifestations of acute leukemia in children.^{4,7,9–11}

The objectives of this study were to identify the frequency of patients of Acute lymphoblastic leukemia (ALL) who presented to the orthopedic department, to determine the frequency of initial orthopedic

manifestations in all patients, and to identify the frequency of patients with normal peripheral smear and normal systemic findings, with these initial orthopedic manifestations.

2. Materials and methods

Two hundred and fifty consecutive patients, with well-recorded data identified from disease code and medical record, were diagnosed with acute lymphoblastic leukemia between January 2004 and December 2016. Medical records were reviewed, with particular attention to the presence of orthopedic manifestations preceding the diagnosis of leukemia. The patients who primarily presented to the orthopedic departments were identified. The patients with orthopedic manifestations were reviewed in detail for musculoskeletal involvement, systemic involvement, and laboratory data. Patients presenting at our hospital with other chief complaints were excluded from the study, even if musculoskeletal symptoms appeared later in the course of the disease.

Twenty-two patients initially presented with orthopedic complaints but were subsequently diagnosed with acute lymphoblastic leukemia. The mean age at the first visit was 5.63 years (range-2-15 years). Thirteen patients were boys, and nine patients were girls. The average follow-up was 3.6 years (range: 2–6 years).

All patients were reviewed retrospectively, and particular attention was paid to the clinical findings at presentation and laboratory data.

* Corresponding author Department of Orthopaedics, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, 576104, India.

E-mail address: hiteshshah12@gmail.com (H. Shah).

URL: <http://orcid.org/0000-0002-2940-3108> (H. Shah).

<https://doi.org/10.1016/j.jor.2020.05.022>

Received 12 April 2020; Received in revised form 24 April 2020; Accepted 31 May 2020

Available online 07 June 2020

0972-978X/ © 2020 Professor P K Surendran Memorial Education Foundation. Published by Elsevier B.V. All rights reserved.

The presence of associated physical findings like lymphadenopathy, hepatosplenomegaly, pallor, ecchymosis, etc. was recorded. Initial values of hemoglobin, WBC, platelets, LDH, and peripheral smear were recorded, along with bone marrow aspiration, which was done at the time of diagnosis. The diagnosis was confirmed by bone marrow biopsy.

3. Results

Twenty-two patients presented primarily with Orthopedic complaints. Twelve patients had joint pain as the initial presentation, whereas six patients had bone pain, and four patients had back-pain. Four patients had single joint involvement, and eight patients had multiple joint involvements. Knee joint pain was most commonly seen ($n = 8$), followed by the elbow ($n = 4$), hip ($n = 4$), and ankle ($n = 1$). Two patients had single bone pain, whereas four patients had multiple bone pain. Most children had pain in the legs ($n = 5$), followed by arms ($n = 2$), feet ($n = 2$), and thigh ($n = 1$). Seven patients presented with a limp.

Pallor was observed in 16 patients (72.72%), lymphadenopathy in 15 patients (68.18%), splenomegaly in 16 patients (72.72%), hepatomegaly in 15 patients (68.18%) and ecchymosis in 5 patients (22.72%). Thirteen patients had elevated body temperature (59.09%) of which only four patients had concurrent infections documented (1 case of sepsis, 2 cases of URTI, and 1 case of LRTI). Hemoglobin was decreased in 17 patients (77.27%). Platelets were reduced in 14 patients (63.63%) and increased in 1 patient (4.54%). The mean leucocyte count was reduced in 7 patients (31.81%), increased in 4 patients (18.18%) and normal in 8 patients (36.36%). Fourteen patients (63.63%) had blast cells seen in peripheral smear. Patients were classified by FAB classification – 10 patients (45.45%) were L1, and 12 patients (54.54%) were L2 subtypes. Elevated lactate dehydrogenase was seen in 12 patients (54.54%). Bone scan was done in 8 patients, of which 5 patients (22.72%) were positive.

Six patients presented to the Orthopedics department back-pain ($n = 4$), and pain in the hip region ($n = 2$). All four patients with back-pain had stiffness in the back, and the coin-test was positive (Fig. 1). There was no hepatosplenomegaly. Blood parameters were in the normal limits. Radiographs revealed multiple wedge fractures (Fig. 2). No patient with compression fracture had neurological deficits. Bone

Fig. 1. A four-year girl with one-month history of back-pain and stiffness as seen with presence of coin test. Her blood parameters were normal. Bone marrow biopsy confirmed the diagnosis.

Fig. 2. Spine radiograph of the same child revealed multiple wedge compression fractures of the vertebrae. She was not having neurological deficit.

marrow biopsy revealed the presence of leukemic cells and depletion of normal cells-the other two patients presented with fever and hip pain simulating septic arthritis of the hip joint. Pseudo-paralysis was present in both patients. However, the passive range of movements and ultrasonography for hip joints and abdomen was normal. Radiographs of the pelvis and hip joints were normal (Fig. 3). Hemoglobin, total counts, platelet counts, and erythrocyte sedimentation rates were normal. Bone marrow biopsy showed the features of ALL.

At the most recent follow-up, 18 patients had survived (Fig. 4). Four patients succumbed to neutropenic sepsis and died.

Fig. 3. Normal trabecular pattern and density in the radiograph of a four-year patient who was referred with right hip pain and pseudo-paralysis. Passive range of movements, blood parameters and ultrasonography were normal. Bone marrow biopsy confirmed the diagnosis of ALL.

Fig. 4. Three-year follow-up radiograph of the child in Fig. 1. Back-pain and stiffness improved with the treatment. Vertebral heights have improved.

4. Discussion

Leukemia is a generalized malignant myeloproliferative disorder, often with initial presenting complaints pertaining to the musculoskeletal system.^{2,4} Though bone and joint complications are common, the clinical presentation may mimic other pathological conditions.² This association may lead the patient to seek orthopedic treatment initially. The orthopedist, therefore, must recognize the unusual patterns of presentation that characterize leukemia and maintain a high index of suspicion if the correct diagnosis is to be made promptly.²

We limited our study to those aspects of leukemia that may directly involve the orthopedist. No attempt was made to study the late complications due to immunosuppressive therapy, the response of bone lesions to treatment, or the correlation between musculoskeletal manifestations and life expectancy.

Twenty-two out of 250 patients (8.8%) of ALL in our study presented with initial orthopedic complaints, as against 20.6% by Rogalsky RJ et al.,² 11.6% by Tuten HR et al.⁵ and 7.1% by Kobayashi D et al.⁷

Bone and joint pain is particularly frequent in childhood leukemia and can dominate the clinical presentation, during the onset and the course of the disease. In our study, 12 patients (54.54%) had joint pain as the initial presentation, whereas seven patients (31.81%) had bone pain. Heinrich SD et al.¹² has reported an incidence of bone pain in 40% and joint pain in 31%. But Rogalsky RJ et al.² report a low value of 14.9% extremity pain only. In general, extremity bone pain and arthritic symptoms are more common in children, whereas axial pain is frequent in adults.^{3,13} We compared our study with various studies in the literature (Table 1).

Gallagher DJ et al.³ and Rogalsky RJ et al.² postulate that the reason for bone pain is a massive proliferation of leukemic cells under the periosteum and in the medullary canal. Borzy MS and Ridgway D⁴¹ attributed the cause of bone erosion to IL2 secreting leukemic

lymphocytes. In contrast, Ribeiro RC et al.¹⁰ and Blatt J et al.¹⁴ attributed to parathormone or an “osteoclast activating factor”. Blatt J et al.¹⁴ also proposed the ectopic production of prostaglandin E2 as an additional mechanism.

Joint pain is referred from metaphyseal periosteal lesions rather than direct synovial infiltration of leukemic cells. In response to metaphyseal leukemic lesions, sympathetic effusion occasionally develops.³

In the literature, the incidence of spinal involvement is controversial. But there is an agreement that the spine is less commonly involved than the long bones. In our study, 4 (1.6%) out of 250 patients of ALL had presented with vertebral compression fracture and osteopenia, which is comparable to 5.6% by Rogalsky RJ et al.,² 1.36% by Kobayashi D et al.,⁷ 0.57% by Blatt J et al.,¹⁴ 2.33% by Simmons CR et al.⁴² and 1.6% by Ribeiro RC et al.¹⁰ Kayser R et al.,⁴ Ribeiro RC et al.,¹⁰ Mehrotra S et al.¹¹ reported the most common site of vertebral involvement to be the thoracic and upper lumbar spine. Our patients also had the same levels involved. We were able to identify only one study which had sub-classified the ALL cases as per FAB and mentioned spine involvement in each subtype. In our study, all four patients of vertebral compression fracture belonged to ALL-L2 type. As per the study of Ribeiro RC et al.,¹⁰ cell morphology was L1 in 13 patients and L2 in 2 patients of vertebral compression fracture.

Gallagher DJ et al.³ attributes that the clinical manifestations of acute leukemia are secondary to a decrease in the production of normal blood components. This decrease produces lethargy, pallor, purpura, fever, hepatosplenomegaly, lymphadenopathy, and bleeding. In our study, pallor was observed in 16 patients (72.72%), lymphadenopathy in 15 patients (68.18%), splenomegaly in 16 patients (72.72%), hepatomegaly in 15 patients (68.18%) and ecchymosis in 5 patients (22.72%). However, Meehan PL et al.¹ reported that lymphadenopathy, liver and spleen involvement might be minimal.

Meehan PL et al.,¹ Kobayashi D et al.,⁷ and Jonsson OG et al.⁸ cited the misdiagnosis of the patients with musculoskeletal features. They were not detected for weeks or months because the hematologic values were relatively normal. 77.27% of our patients were anemic, and 63.63% were thrombocytopenic. Tuten HR et al.⁵ observed the incidence of anemia as 100% and thrombocytopenia of 55.56%. Kobayashi D et al.⁷ reported a rate of anemia in 75% and thrombocytopenia in 50%.

In our study, the mean leucocyte count was reduced in 7 patients (31.81%), increased in 4 patients (18.18%), and it was normal in 8 patients (36.36%). Fourteen patients had blast cells seen in peripheral smear (63.63%). But Rogalsky RJ et al.² reports that WBC on peripheral smear increased by 60%, depressed in 35%, and normal in 5%. Kobayashi D et al.⁷ report a blasts percentage of 31.3%. In his study, WBC count was normal in 81.25%, decreased by 12.5%, and increased by 6.25%.

Among the four patients of vertebral compression fracture seen in our study, the peripheral smear was normal in all cases. As per Kayser R et al.,⁴ at the onset of disease, only 10% of children have normal peripheral blood count. If the patient had spinal involvement and a normal leucocyte count, the diagnosis is often unclear.

Lactate dehydrogenase was elevated in 12 patients (54.54%) in our study, whereas a low incidence was obtained as 28.6% by Kobayashi D et al.⁷

As the orthopedist is the primary contact physician for the patient with ALL, he might have the opportunity to examine the patient first. Hence, he can make an early diagnosis before the pediatrician or hematologist. A flow chart algorithm may be useful for the early diagnosis of ALL in children with musculoskeletal pain (Fig. 5). Despite the poor prognosis of the condition, the more initial the diagnosis by an alert orthopedist, the better is the morbidity and mortality.

Accurate diagnosis is hence a challenge in patients with anemia of unknown origin, neutropenia despite suspected sepsis, inconsistent clinical symptoms and course and the presence of the initial orthopedic

Table 1

Comparison of the various study with musculoskeletal manifestation, clinical features and peripheral smear.

Authors	Year	N*	n#	Musculoskeletal manifestation				Clinical features		Peripheral smear
				Single joint pain	Multiple joints pain	Bone pain	Spine	Present	Absent	
Blatt J et al. ¹⁴	1984	350	2	–	1	–	2	2	–	Absent20
Ribeiro RC et al. ¹⁰	1988	1466	24	–	–	–	24	8 (33.3%)	–	–
Jonsson OG et al. ⁸	1990	296	52	–	–	52	–	40%	–	Normal2
Bradlow A et al. ¹⁵	1991	3	1 (33.3%)	–	2 (66.6%)	–	–	2 (66.6%)	–	2 (66.6%)
Ostrov BE et al. ⁵	1993	10	9 (90%)	–	1 (10%)	–	–	–	–	–
Heinrich SD et al. ¹²	1994	107	83	31%	–	40%	–	–	–	–
Meehan PL et al. ¹	1995	2	–	–	–	–	2	–	2	Normal2
Kai T et al. ¹⁶	1996	168	13	12 (92%)	–	–	–	11 (85%)	–	Normal13
Cabral DA et al. ¹⁷	1999	13	6 (46.2%)	–	–	–	1 (7.7%)	6 (46.2%)	–	17%
Trapani S et al. ¹⁸	2000	6	2 (33.3%)	–	3 (50%)	–	–	6	–	1
Kayser R et al. ¹⁹	2000	1	–	–	–	–	1	–	1	Normal
Chell J et al. ²⁰	2001	20	4	3 (75%)	1 (25%)	–	1 (25%)	4 (100%)	–	3 (75%)
Pandya NA et al. ⁹	2001	3	1 (33.3%)	–	–	–	3 (100%)	2 (66.6%)	–	1 (33.3%)
Bjerregaard LL et al. ²¹	2002	1	–	–	–	–	1	1	–	Normal
Kobayashi D et al. ⁷	2005	295	13	4 (30.8%)	2 (15.4%)	2 (15.4%)	4 (30.8%)	10 (76.9%)	–	5 (38.4%)
Maman E et al. ²²	2007	765	240	72 (30%)	–	124 (51.7%)	–	–	–	–
Gupta D et al. ²³	2008	11	11 (100%)	–	–	7 (63.6%)	–	8	–	5 (45.5%)
Sinigaglia R et al. ²⁴	2008	122	47	40 (32.8%)	–	7 (5.7%)	11 (9%)	122 (100%)	Nil	–
Karimi M et al. ²⁵	2008	211	6%	–	–	19%	–	74%	–	–
Marwaha RK et al. ²⁶	2009	762	64	49/49	–	12/49	1/49	44/49 (fever)	–	–
Cohan N et al. ²⁷	2011	1	–	–	–	1	1	1	–	–
Suri D et al. ²⁸	2011	2	1	–	1	–	–	2	–	–
Have N Van Der et al. ²⁹	2012	1	1	–	–	–	–	1	–	Normal
Zombori L et al. ³⁰	2013	166	33	15 (45%)	18 (55%)	4 (12%)	3 (9%)	22 (66.7%)	–	Normal
Riccio I et al. ³¹	2013	328	73	51 (69.8%)	–	5 (6.8%)	11 (15.1%)	12 (16.4%)	–	–
Jones OY et al. ³²	2015	71	74%	–	–	–	–	Rash 15%	–	18 (25%)
Brix N et al. ^{33,34}	2015	286	53	19 (35.8%)	34 (64.2%)	9 (17%)	6%	55%	–	76%
Uemura T et al. ³⁵	2015	1	1	–	–	–	–	1	–	–
Tragiannidis A et al. ³⁶	2016	97	46	–	–	–	–	–	–	–
Kang S et al. ³⁷	2017	158	24	–	–	–	–	24	–	–
Alfaris B et al. ³⁸	2017	2	1	–	–	1	1	1	1	–
Boccuzzi E et al. ³⁹	2018	4	–	–	4 (100%)	–	–	4 (100%)	–	3 (75%)
Li F et al. ⁴⁰	2019	1	–	–	–	–	1	–	1	Normal1
Our study	2020	250	22	4 (18.2%)	8 (36.4%)	6 (27.3%)	4 (18.2%)	16 (72.7%)	–	14 (63.63%)

Fig. 5. Diagnostic workflow to evaluate a child with musculoskeletal pain.

manifestations with absent clinical findings, and normal peripheral smear.

5. Conclusion

Acute leukemia should be considered strongly as a differential diagnosis in children with severe osteoporosis and vertebral fractures. Initial orthopedic manifestations are not uncommon, and the primary physician should maintain a high index of suspicion as a peripheral smear is not diagnostic in all patients.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Amrath Raj B K: Conceptualization, Data curation, Formal analysis. **Kumar Amerendra Singh:** Conceptualization, Data curation, Formal analysis. **Hitesh Shah:** Conceptualization, Data curation, Formal analysis, Writing - original draft.

Declaration of competing interest

The authors declare that they have no conflict of interest.

References

- Meehan PL, Viroslav S, Schmitt EW. Vertebral collapse in childhood leukemia. *J Pediatr Orthop*. 1995;15(5):592–595.
- Rogalsky RJ, Black GB, Reed MH. Orthopaedic manifestations of leukemia in children. [cited 2020 Apr 7]. *J Bone Joint Surg Am*. 1986 Apr;68(4):494–501. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3957974>.
- Gallagher DJ, Phillips DJ, Heinrich SD. Orthopedic manifestations of acute pediatric leukemia. [cited 2020 Apr 7]. *Orthop Clin North Am*. 1996 Jul;27(3): 635–44. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8649744>.
- Kayser R, Mahfeld K, Nebelung W, Grasshoff H. Vertebral collapse and normal peripheral blood cell count at the onset of acute lymphatic leukemia in childhood. [cited 2020 Apr 6]. *J Pediatr Orthop B*. 2000 Jan;9(1): 55–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10647113>.
- Tuten HR, Gabos PG, Kumar SJ, Harter GD. The limping child: a manifestation of acute leukemia. [cited 2020 Apr 6]. *J Pediatr Orthop*. 1998;18(5): 625–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9746414>.
- Ostrov BE, Goldsmith DP, Athreya BH. Differentiation of systemic juvenile rheumatoid arthritis from acute leukemia near the onset of disease. *J Pediatr*. 1993;122(4):595–598.
- Kobayashi D, Satsuma S, Kamegaya M, et al. Musculoskeletal conditions of acute leukemia and malignant lymphoma in children [Internet]. [cited 2020 Apr 7]. *Journal of Pediatric Orthopaedics Part B*. vol. 14. Lippincott Williams and Wilkins; 2005. 156–61. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15812284>.
- Jonsson OG, Sartain P, Ducore JM, Buchanan GR. Bone pain as an initial symptom of childhood acute lymphoblastic leukemia: association with nearly normal hematologic indexes. *J Pediatr*. 1990;117(2 PART 1):233–237.
- Pandya NA, Meller ST, MacVicar D, Atr AA, Pinkerton CR. Vertebral compression fractures in acute lymphoblastic leukaemia and remodelling after treatment. *Arch Dis Child*. 2001;85(6):492–493.
- Ribeiro RC, Pui C-H, Schell MJ. Vertebral compression fracture as a presenting feature of acute lymphoblastic leukemia in children. *Cancer*. 1988;61(3):589–592.
- Mehrotra S, Kumar A, Singh BN. Vertebral compression fracture. An unusual presentation of childhood acute lymphoblastic leukaemia. [cited 2020 Apr 6]. *J Assoc Physicians India*. 1990 Dec;38(12): 943–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2096136>.
- Heinrich SD, Gallagher D, Warrior R, Phelan K, George VT, Macewen GD. The prognostic significance of the skeletal manifestations of acute lymphoblastic leukemia of childhood. *J Pediatr Orthop*. 1994;14:105–111.
- Hustu HO, Pinkel D. 7 lymphosarcoma, Hodgkin's disease and leukemia in bone. [cited 2020 Apr 7]. *Clin Orthop Relat Res*. 1967 May;52:83–94. Available from: <http://journals.lww.com/00003086-196700520-00008>.
- Blatt J, Martini SL, Penchansky L. Characteristics of acute lymphoblastic leukemia in children with osteopenia and vertebral compression fractures. *J Pediatr*. 1984;105(2):280–282.
- Bradlow A, Barton C. Arthritic presentation of childhood leukaemia. *Postgrad Med*. 1991;67(788):562–564.
- Taylor P, Kai T, Ishii E, et al. *Clinical and Prognostic Implications of Bone Lesions in Childhood Leukemia at Diagnosis Clinical and Prognostic Implications of Bone Lesions in Childhood Leukemia at Diagnosis*. July 2015; July 2015:5–10.
- Cabral DA, Tucker LB. *Alignancies in Children Who Initially Present with*. 1999; 1999 53–7.
- Trapani S, Grisolia F, Simonini G, Calabri GB, Falcini F. *Incidence of Occult Cancer in Children Presenting With Musculoskeletal Symptoms : A 10-Year Survey in a Pediatric Rheumatology Unit*. vol. 6. 2000; 2000:348–359 6.
- Kayser R, Mahfeld K, Nebelung W, Graßhoff H. Vertebral collapse and normal peripheral blood cell count at the onset of acute lymphatic leukemia in childhood. *J Pediatr Orthop Part B*. 2000;9:55–57.
- Chell J, Fernandes JA, Bell MJ. *Leukaemia in Childhood*. 2001; 2001:186–189 April 1998.
- Bjerregaard LL, Rosthøj S. Vertebral compression and eosinophilia in a child with acute lymphatic leukemia. *J Pediatr Hematol Oncol*. 2002;24(4):313–315.
- Maman E, Steinberg AE, Stark AB. *Acute Lymphoblastic Leukemia in Children : Correlation of Musculoskeletal Manifestations and Immunophenotypes*. vols. 63–8. 2007; 2007.
- Gupta D, Singh S, Suri D, Ahluwalia J, Das R, Varma N. Arthritic presentation of acute leukemia in children: experience from a tertiary care centre in North India. *Rheumatol Int*. 2010;30(6):767–770.
- Sinaglia R, Gigante C, Bisinella G, Varotto S, Zanesco L, Turra S. Musculoskeletal manifestations in pediatric acute leukemia. *J Pediatr Orthop*. 2008;28(1):20–28.
- Karimi M, Mehrabani D, Yarmohammadi H. The prevalence of signs and symptoms of childhood leukemia and lymphoma in Fars Province. *Southern Iran*. 2008;32:178–183.
- Marwaha RK, Kulkarni KP, Bansal D, Trehan A. Acute lymphoblastic leukemia masquerading as juvenile rheumatoid arthritis: diagnostic pitfall and association with survival. *Ann Hematol*. 2010;89(3):249–254.
- Cohan N, Sarikhani S, Moslemi S, Karimi M. Initial presentation of acute lymphoblastic leukemia with osteoporosis and multiple spontaneous. *Bone Fractures*. 2011;13(1):52–54.
- Suri D, Ahluwalia J. *Arthritic Presentation of Childhood Malignancy : Beware of Normal Blood Counts*. vols. 827–9. 2011; 2011.
- Have N Van Der, Vaidia S, Story C, et al. Differential diagnosis of paediatric bone pain : acute lymphoblastic leukemia. *Leuk Res*. 2012;36(4):521–523. <https://doi.org/10.1016/j.leukres.2012.01.001>. Available from:.
- Zombori L, Kovacs G, Csoka M, Derfalvi B. *Rheumatic Symptoms in Childhood Leukaemia and Lymphoma-A Ten-Year Retrospective Study*. vols. 1–5. 2013; 2013.
- Riccio I, Marcarelli M, Del Regno N, et al. Musculoskeletal problems in pediatric acute leukemia. *J Pediatr Orthop Part B*. 2013;22(3):264–269.
- Jones OY, Spencer CH, Bowyer SL, Dent PB, Gottlieb BS, Rabinovich CE. *A Multicenter Case-Control Study on Predictive*. 2015; 2015.
- Brix N, Rosthøj S, Herlin T, Hasle H. *Arthritis as Presenting Manifestation of Acute Lymphoblastic Leukaemia in Children*. 2015; 2015:821–825.
- Brix N, Hasle H, Rosthøj S, Herlin T. *Characteristics of Children with Acute Lymphoblastic Leukemia Presenting with Arthropathy*. vols. 15–7. 2018; 2018.
- Uemura T, Yagi H, Okada M, Yokoi T, Shintani K, Nakamura H. Elbow septic arthritis associated with pediatric acute leukemia: a case report and literature review. *Eklm Hast ve Cerrahisi*. 2015;26(3):171–174.
- Tragiannidis A, Vasileiou E, Papageorgiou M, Damianidou L, Hatzipantelis E, Gombakis N. *Bone Involvement at Diagnosis as a Predictive Factor in Children with Acute Lymphoblastic Leukemia*. 2016; 2016:227–230.
- Kang S, Im HJ, Bae K, Park SS. Influence of musculoskeletal manifestations as the only presenting symptom in B-cell acute lymphoblastic leukemia. *J Pediatr*. 2017;vol. 182:290–295. <https://doi.org/10.1016/j.jpeds.2016.11.072>. e1. Available from:.
- Alfaris B. Skeletal manifestations of acute lymphoblastic leukemia in two pediatric cases. *MOJ Orthop Rheumatol*. 2017 Jan 5;7(1).
- Boccuzzi E, Ferro VA, Cinicola B, Schingo PM, Strocchio L, Raucci U. Uncommon presentation of childhood leukemia in emergency department. *Pediatr Emerg Care*. 2018;1 00(00).
- Li F, Wang J, Liu A, et al. Prolonged lumbosacral pain as the initial presentation in acute lymphoblastic leukemia in an adult: a case report. *Med Plus*. 2019;98(24):4–8.
- Borzy MS, Ridgway D. Prolonged defects of interleukin-2 production, responsiveness, and receptor expression in patients with acute lymphoblastic leukemia. *Blood*. 1989 May;73(6):1608–1614.
- Simmons CR, Harle TS, Singleton EB. The osseous manifestations of leukemia in children. [cited 2020 Apr 7]. *Radiol Clin North Am*. 1968 Apr;6(1): 115–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/5690091>.