

## Review Article

# Extramedullary manifestations in acute lymphoblastic leukemia in children: a systematic review and guideline-based approach of treatment

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**Abstract:** Objective: Acute lymphoblastic leukemia (ALL) may present with signs and symptoms related to extramedullary involvement, therefore, leads to delayed diagnosis of ALL in children. This study aims to consider the extramedullary manifestations of ALL in children and their proper treatment. Method: The databases were searched for all relevant subjects including “acute lymphoblastic leukemia”, “clinical presentation”, “unusual presentation”, “childhood acute lymphoblastic leukemia”, “presenting features of ALL”, “extramedullary presentation”, and “atypical presentation” from April 1968 to June 2020. The Inclusion criteria for this review study were all cases reported, case series, and studies about extramedullary presentations of ALL in pediatrics. Eighty-seven studies had inclusion criteria. All reported studies were analyzed given their extramedullary presentations, age, sex, treatment option, and prognostic factors. A two-sided *P*-value less than 0.05 was considered statistically significant. Result: In this review study, the extramedullary initial signs and symptoms of ALL were related to musculoskeletal system 17 (19.5%) especially bony symptoms and hypercalcemia. The additional extramedullary presentations of ALL in order of frequency include; renal involvement, 17 (19.5%), hepatic symptom 12 (13.8%), orbital presentation 10 (11.5%), neurologic signs 8 (9%), dermatological manifestations 5 (5.8%), oral presentations 5 (5.8%), hypereosinophilia 5 (5.8%), abdominal manifestation 3 (3.5%), pericardial involvement 2 (2.3%), and the other miscellaneous presentations 3 (3.5%). Conclusion: The clinicians must become familiar with these extramedullary presentations of ALL in pediatrics to avoid the delayed diagnosis of this disease and increase the probable chance of survival by early detection.

**Keywords:** Unusual manifestation, childhood leukemia, extramedullary presentations, ALL, clinical presentation

## Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children accounting for approximately one-third of all childhood cancers, with a survival rate of about 90% [1, 2]. The exact etiology of ALL is unknown. Factors that play an important role in the pathogenesis of leukemia include ionizing radiation, chemicals, drugs, infections, genetic factors, and chromosomal abnormalities [1-3].

The clinical presentations of ALL can be insidious or rapid and vary from days to months.

The most common clinical symptoms of ALL are usually due to bone marrow failure, including leukopenia, thrombocytopenia, and anemia. Thus, the patients may be presented with bleeding, petechia, purpura, fatigue, anorexia, malaise, bone pain usually long bones, pallor, and fever. These symptoms are related to medullary involvement [1-3].

Extramedullary manifestations due to infiltration of leukemic cells may present as lymphadenopathy, which is usually painless, hepatosplenomegaly, which occurs in 68% of patients, and is commonly asymptomatic. The central

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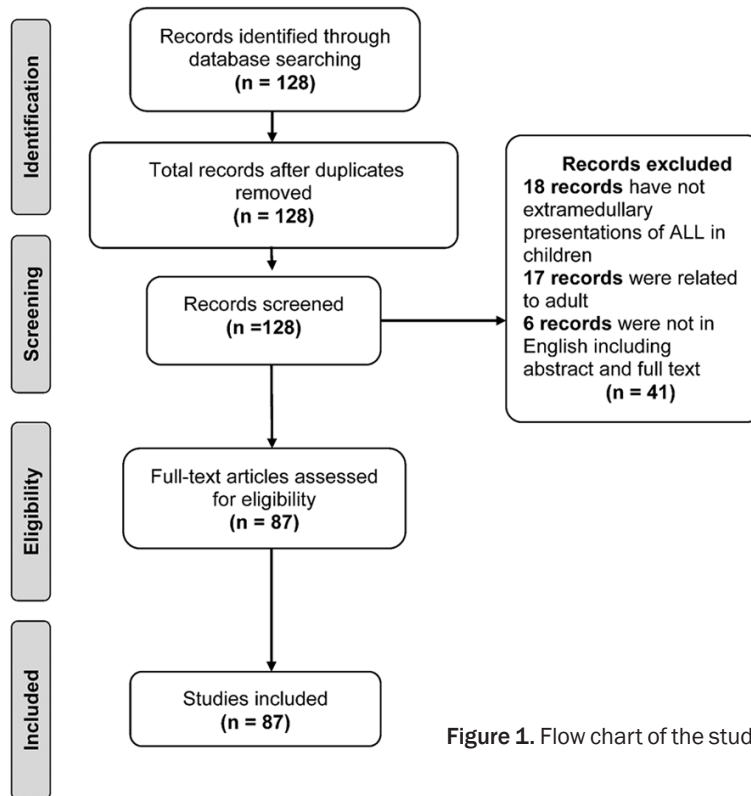


Figure 1. Flow chart of the study.

nervous system (CNS), skin, renal, orbital, and hepatic involvement. Abnormal persistence of any of these common signs and symptoms should be considered as a possible cause of cancer [1, 2, 4].

The infiltration of leukemic cells in the thymus shows itself as an anterior mediastinal mass. It accounts for 10% of newly diagnosed ALL, especially T-cell acute lymphoblastic leukemia (T-ALL) [4].

CNS involvement can manifest as symptoms of increased intracranial pressure, including headache, confusion, and vomiting, seizures, and neck stiffness. Rarely, leukemia may present itself with cranial nerve abnormalities such as trigeminal neuralgia, facial nerve palsy, and neuropathy [5-7].

Testicular enlargement in ALL presents itself as a painless, unilateral mass seen during initial diagnosis in about 2% of the boys. This could be associated with splenomegaly, mediastinal mass, and hyperleukocytosis [8, 9].

About 40% of patients with childhood leukemia initially present with musculoskeletal signs and symptoms as medullary involvement including

limping, bone or joint pain, and bone fracture. Bone pain is a common clinical presentation during initial diagnosis that mainly involves long bones due to leukemic infiltration in the periosteum [10].

Rare extramedullary and endocrinology manifestations infrequently occur in ALL patients, and could mostly transpire in relapse and refractory cases. The locations of extramedullary involvement include; ocular, bone, renal, hepatic, abdomen, bladder, skin, oral, pericardium, and pancreas which are extremely rare during the first presentation [11, 12].

The study aimed to make physicians familiar with the extramedullary presentations of ALL in children, to avoid delayed diagnosis and possibly

increase the chance of survival rate by early detection.

### Methods and materials

#### Study design

To collect relevant articles, major databases (PubMed, Medline, Scopus, Science Direct, Cochrane library, and Google Scholar) were searched for all case report, case series, and articles about presentations of ALL from April 1968 to June 2020. To search for articles, the following keywords were used alone or in combination: “acute lymphoblastic leukemia”, “clinical presentation”, “unusual presentation”, “childhood acute lymphoblastic leukemia”, “presenting features of ALL”, “extramedullary presentation”, and “atypical presentation”. Then the relevant studies were filtered manually.

Each article was reviewed to determine the base of statistical methods used and their appropriateness. All studies were assessed by authors from the aspect of quality assessment, inclusion, exclusion criteria, and eligibility criteria as summarized in the flow chart (Figure 1).

## Extramedullary presentations of ALL

### *Inclusion and exclusion criteria*

The following inclusion criteria were used: studies had to describe extramedullary initial presentations of ALL in children younger than 18 years of age. Articles should have been published between 1968-2020. The articles were written in the English language, if they were not, at least the abstracts were in English. Studies should be the case report, case series, and articles about the extramedullary presentation of ALL in children. Studies that did not indicate extramedullary manifestations or related to medullary involvement of leukemia, or those who were not under the age of 18 years were excluded.

All reported studies were analyzed given their extramedullary presentations, age, sex, treatment option, and prognostic factors.

### *Statistical analysis*

Data were analyzed by SPSS version 23. Descriptive data were presented as mean, standard deviation, frequency, percentages; and also appropriate charts and tables.

## Results

### *Demographic data of studies*

During the last 30 years, from 128 studies, 87 studies had the same inclusion criteria (**Figure 1**). All studies were related to pediatric age groups (age  $\leq 18$  years). The mean age of patients in the selected studies was  $7.3 \pm 4.6$  years (6 months-18 years).

Regarding gender distribution, 57 (65.5%) of all patients were male and 30 (34.5%) were female. The male to female ratio was 1.9:1.

### *The frequencies of the extramedullary presentations*

The detailed features of studies about extramedullary presentations of ALL (n=87) are summarized in (**Table 1**).

The characteristic features of the studies are summarized in **Table 2**. Seventeen studies (19.5%) were related to musculoskeletal system or hypercalcemia as extramedullary presentations of childhood ALL.

The frequency of the extramedullary symptoms related to the musculoskeletal system include vertebral compression, spontaneous fractures, osteoporosis, and hypercalcemia 9 (52.8%), osteomyelitis 1 (5.9%), maxillary mass 1 (5.9%), metaphyseal sclerosis 1 (5.9%), calf pain 1 (5.9%), arthritis 1 (5.9%), Sternal bulging 1 (5.9%), forehead swelling 1 (5.9%), and limping 1 (5.9%). Some cases had two of these extramedullary symptoms. The mean age of children that were presented with initial symptoms related to the musculoskeletal system was  $5.6 \pm 3.6$  years.

The extramedullary presentations of the renal system include 17 studies: renal failure 3 (17.7%), renal mass 2 (12%), hematuria 1 (5.8%), nephromegaly 8 (47.1%), and renal calculi 1 (5.8%), nocturnal enuresis 1 (5.8%), and hemolytic-uremic syndrome 1 (5.8%). The mean age was  $5.31 \pm 3$  years (**Tables 1 and 2**).

The frequency of hepatic involvement includes extramedullary manifestations in children presenting with ALL were 13.8%. The range of hepatic involvement in childhood cases of ALL has included a mild increase in transaminases without jaundice 2 (16.7%), hepatic dysfunction with jaundice 4 (33.3%), or fulminant hepatic failure 6 (50%) (**Tables 1 and 2**).

Neurological symptoms as an extramedullary initial presentation of ALL were included intracranial lesions 2 (25%), and peripheral neuropathies 4 (50%), facial palsy 1 (12.5%), and myopathy (12.5%) with a mean age of  $10.6 \pm 3.5$  years (**Tables 1 and 2**).

Extramedullary ophthalmic presentations of childhood ALL in studies were as follows: orbital mass 3 (30%), visual loss 1 (10%), retinal detachment 1 (10%), ischemic optic neuropathy 1 (10%), and proptosis 4 (40%). The mean age among patients with ophthalmic manifestations was  $6.8 \pm 5.6$  years (**Tables 1 and 2**).

Five studies (5.8%) demonstrated eosinophilia as an initial manifestation of childhood ALL (**Tables 1 and 2**).

Five studies (5.8%) reported skin involvement as an extramedullary presentation of childhood ALL that were as follows: skin nodule 2 (40%), urticarial plaques 1 (20%), atypical pyoderma

## Extramedullary presentations of ALL

**Table 1.** The detailed features of studies about extramedullary presentation of childhood ALL

N	Author	Sex	Age	Location	Presentation	Ref
1	Samuda GM	M	7	Musculoskeletal	Vertebral Compression and back pain	[103]
2	Söker M	M	3	Musculoskeletal	Spontaneous Humeral Fracture and Osteoporosis	[104]
3	Kumar R	M	3	Musculoskeletal	Metaphyseal sclerosis	[105]
4	Türker M	F	14	Musculoskeletal	Hypercalcemia	[20]
5	Sadawaite S	M	3	Musculoskeletal	Multiple pathological Fractures, generalized osteopenia and vertebral compression	[12]
6	Hafiz MG	M	9.5	Musculoskeletal	Back pain and vertebral compression	[106]
7	Zhang Y	F	9	Musculoskeletal	Maxillary mass	[107]
8	Cohan N	M	4	Musculoskeletal	Osteoporosis and fractures	[27]
9	Duarte-Salazar C	M	6	Musculoskeletal	Arthritis	[108]
10	Teran CG	M	11	Musculoskeletal	Calf pain	[109]
11	Bahoush G	M	6	Musculoskeletal	Severe hypercalcemia	[22]
12	Martins AL	M	3	Musculoskeletal	Severe hypercalcemia	[23]
13	Poirée M	M	2	Musculoskeletal	Life-threatening hypercalcemia	[21]
14	Zareifar S	M	3.5	Musculoskeletal	Sternal bulging	[110]
14	Shakibazad N	F	6	Musculoskeletal	Left femoral pain and Limping	[111]
16	Hanapi MS	F	1	Musculoskeletal	Forehead Swelling	[112]
17	Tavil B	M	2	Musculoskeletal	Chronic recurrent multifocal osteomyelitis	[113]
18	Segal I	M	8.5	Hepatic	Abnormal Liver Transaminases	[49]
19	Kader A	F	4	Hepatic	Fulminant hepatic failure	[46]
20	McCord RG	M	5	Hepatic	Fulminant hepatic failure	[50]
21	Conway EE	F	5	Hepatic	Fulminant hepatic failure	[51]
22	Devictor D	M	14	Hepatic	Fulminant hepatic failure	[47]
23	Kelleher JF	M	9.5	Hepatic	Hepatic dysfunction	[52]
24	Alvaro F	F	6	Hepatic	Jaundice	[53]
25	Mori T	F	14	Hepatic	Jaundice	[48]
26	Litten JB	M	4	Hepatic	Fulminant hepatic failure	[54]
27	Gu RL	M	15	Hepatic	Fulminant hepatic failure	[55]
28	Heincelman M	M	18	Hepatic	Hepatitis	[57]
29	Ford J	M	7	Hepatic	Cholestatic jaundice	[56]
30	Jones DP	F	12.3	Renal	Renal failure	[34]
31	Jayagopal S	M	5	Renal	Hyperechoic renal cortical masses	[37]
32	Martins A	F	0.5	Renal	Nephromegaly	[39]
33	Marwaha RK	F	7	Renal	Hematuria	[114]
34	Asdahl PH	M	10	Renal	Acute renal failure	[36]
35	Daly GF	M	5	Renal	Renal calculi	[35]
36	Otsubo K	F	6	Renal	Nocturnal enuresis	[44]
37	Pradeep R	M	7	Renal	Bilateral nephromegaly	[43]
38	Ali SH	M	6	Renal	Bilateral renal enlargement	[115]
39	Boueva A	F	1.7	Renal	Bilateral nephromegaly	[41]
40	Escobar H	F	6	Renal	Acute renal failure	[38]
41	Martini G	F	8	Renal	Hemolytic-uremic syndrome	[45]
42	Prada Rico M	M	3	Renal	Bilateral nephromegaly	[116]
43	Erdem E	F	5	Renal	Nephromegaly	[42]
44	Arora SK	F	1.3	Renal	Nephromegaly	[40]
45	Sherief LM	F	2.5	Renal	Bilateral renal enlargement	[33]
46	Thakore P	M	4	Renal	Bilateral renal masses	[117]

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47	Liu HC	M	10	CNS	Acute sciatica	[58]
48	Kraigher-Krainer E	M	11	CNS	Sensory neuropathy	[7]
49	Forester CM	F	13	CNS	Intracranial mass	[61]
50	Gokce M	M	7	CNS	Intracerebral metastasis	[59]
51	Chaudhuri T	M	18	CNS	Trigeminal neuralgia	[62]
52	Nishimura M	F	7	CNS	Meralgia paresthesia	[60]
53	Kameda G	F	9	CNS	Myopathy	[64]
54	Karimi M	M	10	CNS	Facial palsy	[63]
55	Humayun M	M	1.5	Orbit	Orbital mass	[69]
56	Kaikov Y	M	1.5	Orbit	Visual loss	[70]
57	Yuh WT	F	4	Orbit	Intraorbital tumor	[68]
58	Tang RA	M	15	Orbit	Retinal detachment	[72]
59	Chaudhuri T	M	18	Orbit	Ischemic optic neuropathy	[71]
60	Shahriari M	M	5	Orbit	Unilateral proptosis	[74]
61	Murthy R	F	6	Orbit	Proptosis	[75]
62	Kiratli H	F	9	Orbit	Proptosis and chemosis	[118]
63	Sathitsamitphong L	F	3	Orbit	Orbital Mass	[119]
64	Sivaperumal PR	M	5	Orbit	Bilateral Proptosis	[76]
65	Nath UK	M	14	Abdomen	Acute abdomen	[95]
66	Shahriari M	M	5	Abdomen	Acute appendicitis	[96]
67	Delhi Kumar CG	M	7	Abdomen	Intussusception	[97]
68	Rezamand A	M	5	Blood	Eosinophilia	[120]
69	Ferruzzi V	M	11	Blood	Eosinophilia	[84]
70	Parasole R	F	7.5	Blood	Eosinophilia	[82]
71	Wynn TT	F	5	Blood	Eosinophilia	[81]
72	Yamaoka M	M	3	Blood	Eosinophilia	[80]
73	Aronovich S	M	18	Oral	Gingival pain	[90]
74	Kulkarni KP	M	5	Oral	isolated parotid involvement	[93]
75	Shahriari M	M	8	Oral	Right palatal erosion	[91]
76	Sneha LM	M	8	Oral	Bilateral parotidomegaly	[92]
77	Katz J	M	6	Oral	Trismus	[94]
78	Jiang X	M	5	Skin	Skin nodule	[86]
79	Chien AJ	M	10	Skin	Urticarial plaques	[85]
80	Bakhshi S	M	2	Skin	Atypical pyoderma gangrenosum	[88]
81	Anderson PC	F	0.5	Skin	Isolated scalp nodule	[87]
82	Jaing TH	F	11	Skin	Cutaneous lymphocytic vasculitis	[89]
83	Ozdemir R	M	7	Pericardium	Pericardial effusion	[99]
84	Battle CU	F	6	Pericardium	Pericarditis	[98]
85	Valizadeh M	M	18	Thyroid	Thyroid nodule	[100]
86	Sahoo RK	M	18	Pleural	Chylothorax	[102]
87	Gökçe M	M	13	Metabolic	Lactic acidosis	[101]

gangrenosum 1 (20%), and cutaneous lymphocytic vasculitis 1 (20%) (**Tables 1 and 2**).

Moreover, five studies reported oral involvement as the extramedullary presentation of childhood ALL that were as follows: parotid involvement 2 (40%), gingival pain 1 (20%), tris-

mus 1 (20%), palatal erosion 1 (20%) (**Tables 1 and 2**).

Three studies demonstrated abdominal symptoms as extramedullary involvement including acute abdomen 2 (66.7%) and intussusception 1 (33.3%) (**Tables 1 and 2**).

## Extramedullary presentations of ALL

**Table 2.** The frequency of extramedullary initial presentations of ALL in studies

Locations	N (Studies)	Frequency of cases	M:F Ratio	Mean of ages (y) ± SD
Musculoskeletal symptoms	17	19.5%	3:1	5.6±3.6 (1-14 Y)
Renal symptoms	17	19.5%	0.7:1	5.31±3 (0.5-12.3 Y)
Hepatic symptom	12	13.8%	2:1	9.2±4.9 (4-18 Y)
Ophthalmic symptoms	10	11.5%	1.5:1	6.8±5.6 (1.5-18 Y)
Neurological symptom	8	9%	1.6:1	10.6±3.5 (7-18 Y)
Eosinophilia	5	5.8%	1.5:1	6.3±3 (3-11 Y)
Skin involvement	5	5.8%	1.5:1	5.7±4.7 (0.5-11 Y)
Oral symptom	5	5.8%	5:1	9±5.2 (5-18 Y)
Abdominal symptom	3	3.5%	3:1	8.6±4.7 (5-14 Y)
Cardiac Symptom	2	2.3%	1:1	6.5±0.7 (6-7 Y)
Miscellaneous	3	3.5%	4:1	12.7±7.5 (2-18 Y)
Lactic Acidosis				
Chylothorax				
Thyroid Nodule				
<b>Totally</b>	<b>87</b>	<b>100%</b>	<b>1.9:1</b>	<b>7.3±4.6 (0.5-18 Y)</b>

SD: Standard Deviation, N: Number of Patients, Y: Years Old.

Pericardial involvement was observed in two cases of ALL, who presented with pericarditis and pericardial effusion as an extramedullary presentation (**Tables 1 and 2**).

The other miscellaneous extramedullary presentations of childhood ALL also include acute thyroid mass (one study), lactic acidosis (one study), and chylothorax (one study) (**Tables 1 and 2**).

### Discussion

Childhood ALL may present with signs and symptoms related to extramedullary involvement, which could lead to delayed diagnosis [11, 12]. The mean age of patients in reported cases with extramedullary initial presentations in ALL was 7.3±4.6 years. The peak incidence of ALL is between the ages of 2 to 5 years, and it is more prevalent in boys [13, 14]. In this review, male predominance was observed with a male to female ratio of 1.9:1, which was similar to other studies [2, 14]. In our review, the age of diagnosis was slightly higher than most studies [2, 14, 15]. It can be inferred that age is marginally higher in ALL patients with extramedullary initial presentations.

In this review, among the extramedullary presentations of ALL, most of them were related to musculoskeletal system 17 (19.5%) and renal involvement 17 (19.5%) (**Table 2**). The mus-

culoskeletal symptoms in our study mostly include vertebral compression, spontaneous fractures, osteoporosis, and hypercalcemia (**Table 1**). Several studies show that the prevalence of musculoskeletal manifestations as an initial presentation in childhood ALL was estimated between 11.6 and 50% [16-19]. In our study analysis, the prevalence was 19.5%.

The prevalence of hypercalcemia of malignancy in pediatrics is 0.4-1.3%, (both solid and hematologic malignancies of childhood), which is more common in ALL than myeloid leukemia, commonly associated with translocation (17; 19). The mechanisms of hypercalcemia of malignancy are humoral factors like parathyroid hormone-related peptide (PTHrP), and osteolysis related to metastatic cancer. The production of PTHrP and transforming growth factor-beta (TGF-β) by malignant cells stimulate osteoclastic resorption and renal reabsorption of calcium, resulting in hypercalcemia. The management includes corticosteroid, intravenous hydration, calcitonin, bisphosphonates, and denosumab and initiation of chemotherapy without delay. In the refractory form of hypercalcemia of malignancy, hemodialysis may be indicated [20-25].

In our study, spontaneous fractures were other initial rare musculoskeletal manifestations of ALL. A study of Hessling et al. reported early radiographic findings, usually as metaphysical transverse lucent bands with or with-



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out bony changes such as periosteal reaction in 9% of leukemia patients [26]. The pathogenesis of fractures and vertebral compressions in leukemia include decreased bone mineral density by leukemic cell infiltration in bones or soluble factors produced by malignant cells like the tumor necrosis factor (TNF), osteoclast activated factor, lymphotoxin, and Interleukin-1. Treatment includes initiation of chemotherapy without delay with orthopedic consultation [27-29].

Renal presentations in 17 (19.5%) were another most common extramedullary presentation of childhood ALL that among them nephromegaly was more prevalent than others. The frequency of nephromegaly and renal involvement varies in ALL patients. It is reported to be between 2 and 24% in several studies [30-33]. In our study analysis, the prevalence was 19.5%.

In our study, renal presentations of ALL include acute renal failure, renal calculi, renal mass, hematuria, nephromegaly, nocturnal enuresis, and hemolytic uremic syndrome. In this study, renal dysfunction was more frequently seen in T cell ALL but was not considered as a prognostic factor. Uric acid nephropathy usually occurs after chemotherapy in cancer patients, but it rarely happens as an initial presentation [34, 35]. Two mechanisms for renal failure in childhood ALL are described. First, the infiltration of leukemic cells in the renal interstitium, which leads to vascular stasis and reversible damage to the nephron. Second, tumor lysis syndrome is another mechanism that induces renal failure in ALL patients [36]. Leukemic renal infiltration usually is hypoechoic, but in this review, hyperechoic infiltration was noted as an ALL manifestation. Acute renal failure was another renal symptom, which was frequently reported as an initial presentation of ALL. The treatment of childhood ALL with acute renal failure is an initiation of chemotherapy without delay and in cases, with electrolyte imbalances or tumor lysis syndrome, close monitoring is essential and be careful in patients with severe electrolyte disorders dialysis should not be delayed [33, 36-38].

Renal calculi are another extramedullary renal presentation of ALL which, is frequently seen with T cell type, and occur in association with

spontaneous tumor lysis syndrome [35]. In this study, the renal stone was of uric acid type due to high serum uric acid.

Nephromegaly was also due to leukemic cell infiltration and was associated with hyperuricemia and pyelonephritis. Nephromegaly has no prognostic significant [39]. Leukemic infiltration of the kidney could be a diffuse or nodular pattern, but in childhood ALL, the diffuse pattern is more common. Moreover, nephromegaly may be either unilateral or bilateral. It rarely may be accompanying hypertension and electrolyte imbalance [40-43]. Enuresis can be instigated by several conditions, and hypercalciuria caused by hypercalcemia may lead to nocturnal enuresis by augmented osmotic load [44]. The hemolytic uremic syndrome can be an initial manifestation of childhood ALL. The main suggestive pathogenesis seems to be the destruction of renal microcirculation with glomerular endothelium lesions persuaded by cytokines like tumor necrosis factor (TNF $\alpha$ ), interleukin-6, interleukin-1, and interleukin-8. These cytokines that may also be released from leukemic cells are supposing an important role in hemolytic uremic syndrome pathogenesis [45].

Hepatic presentations of childhood ALL include hepatitis, liver dysfunction, jaundice, and acute hepatic failure. The frequency of hepatic involvement in our study was 13.8%. Although several studies reported that hepatic involvement at the initial presentation of childhood ALL is extremely rare [46-48]. Hepatomegaly is frequently seen as the initial presentation of childhood ALL, but acute liver failure is rare. Several mechanisms are suggested to describe the pathogenesis of fulminant hepatic failure in childhood ALL including comorbid sepsis, viral infections, or hepatic ischemia caused by blockade of hepatic blood flow by infiltrating leukemic cells. The necrosis of hepatic cells may lead to the accumulation of ammonia and toxic material in the body and deteriorate encephalopathy and consequently exacerbate tumor lysis syndrome. The management of ALL in the setting of encephalopathy includes early hemofiltration and starting corticosteroid with dose modification of vincristine and if needed daunorubicin. Some experts suggested that starting corticosteroid and supportive care to prevent tumor lysis syndrome and when the

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patient recovers from encephalopathy start chemotherapy with full doses [46-57].

The neurological presentations of ALL include neuropathy (acute sciatica, trigeminal neuralgia, facial palsy, meralgia paresthesia or thigh pain, and numb chin syndrome), intracranial masses, and myopathy [58-64]. Therefore, in our study neuropathy was the main cause of the extramedullary neurological symptom of childhood ALL. The prevalence of CNS involvement in childhood ALL in our review study was about 9%. Since other studies revealed that the prevalence of CNS involvement reported between 3%-40% [65-67].

Numb chin syndrome is a pure sensory neuropathy of the inferior alveolar nerve at the mandibular area. The pathogenesis of numb chin syndrome in leukemia includes two categories: intracranial and extracranial. Extracranially, the mechanical nerve compression by mandibular bone involvement or by tumoral infiltration of the nerve sheath was the basis of pathogenesis. Intracranially, the involvement of the trigeminal nerve root by malignant meningioma or the infiltration of leukemic cells into the trigeminal nerve was the basis of pathogenesis [7].

The etiology of trigeminal neuralgia and cranial nerve palsies (third, fourth, and sixth) as the rare initial presentations of ALL were probably due to leukemic deposit in the cavernous sinus [6].

CNS involvement by leukemia has been detected at diagnosis in less than 5% of children with ALL. The treatment of CNS involvement includes high-risk chemotherapy plus radiotherapy [5]. Leukemic intracranial mass was seen commonly in acute myeloid leukemia as granulocytic sarcoma or chloroma, but it can be seen in ALL. Leptomeningeal invasion by leukemic cells can be either focal or diffuse, while in a focal invasion, it can mimic intraparenchymal tumors [59, 61]. The diagnosis of a leukemic brain tumor may be difficult, particularly if CSF evaluation does not reveal blast cells. Leukemic cells initially infiltrate the wall of the superficial arachnoid veins and then penetrate to deeper arachnoid veins placed in white and gray matter. The obstruction of arachnoid villi blocks CSF circulation, which leads to increased intracranial pressure (ICP).

When ICP increases, patients generally have neurologic findings including headache, blurred vision, and decreased level of consciousness that necessitate imaging and CSF study [5, 59, 61, 63]. Adjacent meningeal involvement of the nerve and direct leukemic infiltration of the temporal bone and tympanic cavity and can lead to damage to the facial nerve in childhood ALL. The treatment includes chemotherapy and radiotherapy [63].

In our reviewed articles, the frequency of orbital presentations as an extramedullary initial presentation in ALL was 11.5%, including intra-orbital masses, optic neuropathy, decreased vision, retinal detachment, and unilateral or bilateral proptosis [68-76].

The differential diagnosis of proptosis and orbital mass in children include; orbital cellulitis, capillary hemangioma, dermoid cyst, hyperthyroidism, congenital abnormalities such as Gruber's or Crouzon's syndrome, and malignancy such as rhabdomyosarcoma, retinoblastoma, optic glioma, chloroma of myeloid leukemia, lymphoma, histiocytosis, Ewing sarcoma, esthesioneuroblastoma as well as metastases [74, 77-79].

ALL as a cause of orbital mass is extremely rare. The MRI finding was approximately distinctive with the iso-intensity of gray matter in T1 and T2 weighted images [68, 69]. The mechanisms of decreased vision and optic nerve edema in pediatric ALL is not well-known but could be due to obstruction of venous drainage by perivascular infiltration of leukemic cells. Blurred vision and optic nerve swelling were seen more commonly with T cell ALL [68, 70, 71].

Leukemic infiltration of the choroid and retinal detachment is another initial manifestation of ALL and it could be related to the high vascularity of choroid [72]. The treatment of childhood ALL presenting with orbital nerve involvement include chemotherapy and radiotherapy to the optic nerve if vision is at risk [70, 71].

Eosinophilia as the initial presentation in childhood ALL with high white blood cell is rare and is a poor prognostic sign [80]. The prevalence of eosinophilia in our study as an initial presentation of childhood ALL was 5.8%. The exact



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pathogenies are not well known but evaluation of blast cell for cytogenetic abnormality is very important because eosinophilia in childhood ALL may be accompanying chromosome 5 deletion and translocation (5, 14) that worse the prognosis of the patients. The treatment includes higher risk chemotherapy if the patients had a cytogenetic abnormality. Additionally, because of the thrombotic event with severe eosinophilia, we can start enoxaparin in the induction phase and interrupt it when platelet count comes below 30000 cell/ $\mu$ l [80-85].

Skin involvement is also an extramedullary manifestation of childhood ALL with a prevalence of 5.8% in our review study. The dermatological manifestations of childhood ALL in our study were include skin nodule, urticarial plaque, pyoderma gangrenosum, and cutaneous vasculitis. The appearances of leukemia cutis, due to the infiltration of leukemia cells, are variable and including plaques, nodules, ulcers, and papules. Swellings and vesicles are rare presentations, and the locations are usually the trunk, scalp, extremities, and sites of herpetic lesions. Although some study reports a poor prognosis of leukemia cutis, the treatment includes chemotherapy and rarely in refractory cases may radiotherapy be needed [86, 87].

The patient also may present with urticarial plaque which may be due to leukemic infiltration or hypereosinophilia [85]. Pyoderma gangrenosum and cutaneous lymphocytic vasculitis are reported as an extramedullary dermatological manifestation of childhood ALL [88, 89].

Oral manifestations of childhood ALL in our review study had a frequency of 5.8%. They include parotid involvement, gingival pain and bleeding, palatal erosion, and trismus. The pathogenesis of parotid enlargement is due to leukemic cell infiltration and all childhood ALL that present with parotidomegaly are CD10 positive ALL. The treatment is starting chemotherapy. The patients presenting with the oral or dental problem must be visited by a pediatric dentist before starting chemotherapy [90-94]. Trismus can be due to the infiltration of the leukemic cells around the trigeminal nerve [94].

Excessive gingival bleeding, pericoronitis, and palatal erosion that is resistant to regular treatment can raise the possibility of systemic disease like ALL since it needs a high index of suspicion to prevent delayed diagnosis [90, 91].

Another extramedullary presentations of ALL in children include acute abdomen and intussusception that leading to surgery was due to acute appendicitis or splenic infarction related to leukemic infiltration of the spleen or appendix in childhood ALL [95-97].

The involvement of pericardium as a presentation of ALL was identified in two (2.3%) of our reported cases. It can manifest as pericardial effusion, pericarditis, and cardiac tamponade, which could be a direct effect of leukemic infiltration [98]. Pericarditis and pericardial effusion were seen as an initial presentation in 4-7% of all the patients with malignancy. The treatment is to start chemotherapy and corticosteroid [98, 99].

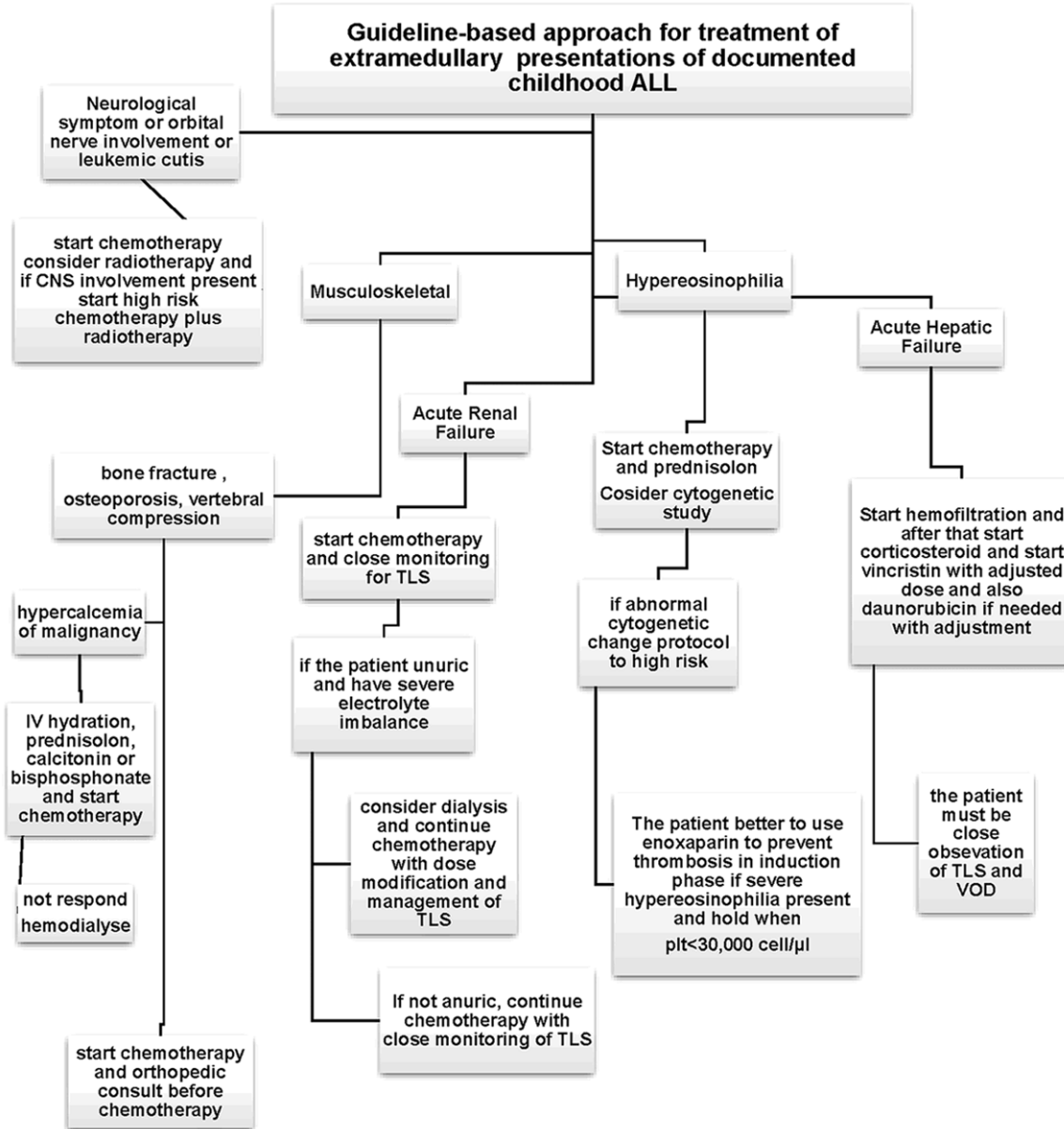
The other extramedullary presentations of childhood ALL in children with less frequency are thyroid mass, lactic acidosis, and chylothorax [100-102].

Chylothorax can be due to obstruction of the lymphatic system in tuberculosis. If there is no evidence of obstructed lymphatic system by lymph node enlargement, the possibility of ALL should be kept in mind. For example, a case with the co-existence of tuberculosis and ALL that was presented with chylothorax [102].

Unexplained lactic acidosis may occur secondary to malignancy. Our review study showed a case of lactic acidosis as a presentation of ALL in children. Serum TNF and insulin-like growth factors play an important role in the overproduction of lactate by leukemic cells. Other possible mechanisms of lactic acidosis include decreased hepatic and renal perfusion by leukemic infiltration that leads to delayed excretion and decreased filtration [101].

Thyroid involvement in pediatrics with ALL as initial extramedullary manifestation is rare. In our study, a patient with a thyroid nodule and normal thyroid function due to infiltration of leukemia was reported [100]. **Figure 2** shows the guideline-based approach for the

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**Figure 2.** The guideline-based approach for treatment of extramedullary presentations of ALL. TLS: tumor lysis syndrome, VOD: Veno occlusive disorder, CNS: central nervous system.

treatment of extramedullary presentations of childhood ALL.

### Conclusions

The clinicians must become familiar with these extramedullary presentations of ALL in pediatrics to avoid the delayed diagnosis of this disease and increase the probable chance of survival by early detection. Moreover, this review can help pediatric oncologists to treat child-

hood ALL presenting with extramedullary involvement with better knowledge.

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### Disclosure of conflict of interest

None.

### Abbreviations

ALL, Acute Lymphoblastic Leukemia; CNS, Central Nervous System; CSF, Cerebro-spinal Fluid; ICP, Intracranial Pressure; TGF- $\beta$ , Transforming Growth Factor Beta; TNF, Tumor Necrosis Factor.

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