Introduction

The expected incidence of cancer in children under 15 years is 110-150/1,000,000 children a year, being slightly more common in men\(^1\). Leukemia is the most commonly encountered cancer and accounts for around 35-40% of all cancers at that age\(^1\). U.S. statistics establish an incidence rate of one case of leukemia every 7,000 children per year\(^2\).

In Chile, the preliminary report of the National Registry of Childhood Cancer Population (RENCI) revealed in 2007 an incidence of leukemias of 42.7/1,000,000\(^1\). Since the beginning of the Program Cancer in the Child in 1988, an average of 100-110 new cases of lymphoblastic leukemia and 30 cases of myeloid leukemia per year have been reported in the public health sector\(^1\).

The signs and symptoms that suggest leukemia are varied and recommendations for diagnostic suspicion are clearly detailed in the Clinical Guide: Leukemia in Children Under 15 years, Chilean Ministry of Health\(^1\).

In general, diagnosis should be suspected in any child with anemia not associated with bleeding, fever...
associated or not with pallor, visceromegaly and CBC with anemia and/or neutropenia (sometimes leukocytosis), bone pain not associated with trauma, with CBC with cytopenia.

Leukemia should be included in the differential diagnosis in the presence of combination of the following signs and symptoms: Fever of unknown origin; bone pain not associated with trauma; spontaneous bruising or associated with minor trauma; nasal or gingival bleeding; recurrent infections; lymphadenopathy (persisting for more than 4 weeks; lymph nodes larger than 3 cm; generalized palpable lymph nodes), and splenomegaly(1-4).

There are genetic as well as environmental factors associated with its pathogenesis. Clearly, there is an increased risk associated with genopathies such as Klinefelter syndrome and Down syndrome, the latter posing a relative risk 15 times higher than that faced by the general population (2.3). Exposure to chemicals, such as benzene, pesticides and ionizing radiation are modifiable factors involved in its etiology(2).

Acute lymphoblastic leukemia (ALL) is defined by the presence of more than 20% lymphoblasts in bone marrow(3,4) and represents the most common type of leukemia in childhood, accounting for 80% of cases(3,4) It predominates in men and occurs most often between the ages of 2 and 5 years(3,4).

Acute myeloid leukemia (AML) represents 17% of leukemias(2). Its occurrence is similar in both sexes with no predominance for any given age range(4).

Initial clinical manifestations are usually nonspecific and the most common clinical presentation includes: pallor, fatigue, bleedings, fever and recurrent infections as a result of an existing spinal cord dysfunction(2,4). The CBC may reveal anemia, thrombocytopenia and/or neutropenia with normal, decreased or increased WBC count(3,4). In 95% of cases, ALL manifests itself with some cytopenia in the CBC, whilst anemia is present in 99% of cases. The WBC is normal in 50% of children(3), being anemia the alarm symptom in these cases.

In AML, 44% of patients present with anemia at diagnosis, while 69% has neutropenia and 25% exhibits leukocytosis with CBC count over 100.000/microliter(3); complications such as cerebral, lung and liver infarction as a result of leukocytosis may be present(1,3).

Although definitive diagnosis is achieved by studying the bone marrow, the imaging study, mainly in patients with bone pain and extramedullary involvement, may provide the clinician with valuable complementary information when the first symptoms derive from tissue infiltration and involvement of haematological series appears discrete and asymptomatic.

The chance of cure depends on the type of leukemia, the presence of associated adverse factors and the response to treatment, being about 73% for lymphoblastic leukemia and 50% for myeloid leukemia(1).

The purpose of this paper is to review the initial radiological manifestations of leukemia in children. Whereas it is a systemic disease, the goal is to identify the key elements in the study of the various organs involved, thus allowing the radiologist to suspect diagnosis in the early stages of the disease.

Late-stage alterations or treatment complications, such as osteonecrosis, infections by opportunistic pathogens, graft-vs host disease, etc., where magnetic resonance imaging (MRI) and computed tomography (CT) play a fundamental role will not be reviewed.

**Leukemia. Bone and extramedullary manifestations**

Due to extramedullary tissue infiltration, visceromegaly (hepatomegaly, splenomegaly, nephromegaly, enlargement of the pancreas), polyadenopathies, central nervous, renal and testicular system involvement may be observed(1,3,4), the latter being the least common pathology. Its frequency varies depending on the type of leukemia.

Imaging findings on those most frequently affected organs, will be reviewed.

**Liver, spleen, kidneys**

An estimated 60-70% of patients with ALL present with hepatosplenomegaly(3), while AML occurs in no more than half of the cases(5). It is often a finding on physical examination and rarely causes functional impairment(1). Bilateral nephromegaly is also a common finding, though less frequent.

Ultrasonography (US) studies allow depiction of increased size of these organs, which may be associated with decreased liver and splenic parenchymal echogenicity and increased echogenicity of the renal parenchyma, conditions that can be reversed with treatment(6,7) (Figure 1). Along with nephromegaly, CT scans reveal multiple low-attenuation areas in the renal parenchyma, usually presenting bilaterally(7,8) (Figure 2).

**Figure 1. Six-month infant with ALL. Abdominal ultrasound revealed bilateral nephromegaly. On a sagittal section of the right flank, enlarged kidney on that side (sagittal diameter of 9.0 cm) and slightly increased echogenicity are observed.**
Lymphadenopathies

The involvement of cervical, axillary and/oringuinal nodes occurs in up to 50% of patients with ALL and in 25% of patients with AML(3,5). Ultrasound is useful in the study of lymph nodes, since along with confirming their presence it allows their appropriate characterization(9,10).

Generally, adenopathies associated with hepatosplenomegaly(9), are painless, fast growing, local or generalized(10). Lymph nodes hard in consistency, with anteroposterior diameter greater than 1.0 cm in cervical and axillary nodes and greater than 1.5 cm in the inguinal region are considered as suspicious(9).

The normal oval nodal morphology may be preserved or may exhibit a more rounded shape; they are commonly grouped in bunches(9). Lymph nodes are usually hypoechoic and nodal hilum may be absent or eccentrically placed due to tumor invasion(10,11). On color Doppler studies it usually shows hiliar vascular flow within it. Though none of the aforementioned signs is pathognomonic of leukemia, their presence in the appropriate clinical context increases the index of suspicion(11).

Bone involvement

Bone pain is the most commonly encountered symptom secondary to proliferation of neoplastic cells in the bone marrow(7,12,13).

An estimated 30% of patients with ALL present with bone pain(4) and sometimes this may be the only alarm symptom in the presence of a CBC without leukocytosis, which may occur in 1% of cases(3). It may affect any part of the skeleton, being the pelvis, vertebrae and long bones of lower extremities the most commonly affected sites(3).

Clinically, pain is usually insidious in onset, constant, not related to physical activity and exacerbated at night, progressive in intensity and refractory to the use of analgesia. It may be accompanied by claudication and rarely presents initially with pathological bone fractures(4,13).

Though unusual, it may occur as migratory oligoarthralgies of large joints, asymmetrically distributed, with or without arthritis. Similarity with diseases such as juvenile idiopathic arthritis may cause a delay in diagnosis of leukemia(13).

Despite the wide variety of imaging methods currently available, simple radiography remains the initial method of choice for evaluation of bone pain(14).

An estimated 50-70% of patients with leukemia reveal evident bone changes on radiographic studies at diagnosis(15,16).

These alterations encompass:

1. Radiolucent, fine, transverse metaphyseal bands. They represent the most common finding suggestive of preschool children leukemia. In patients under 2 years of age, their specificity decreases, and may be found in other chronic diseases that also alter osteogenesis(6,12,15). They are usually located in the proximal and radio distal humerus, and distal femur(7,14), the latter being the most frequent site(7,13) (Figures 3 and 4).

2. Local or diffuse osteopenia, that may present with back pain or lumbar pain due to vertebral crushing(6,17) (Figure 5).

3. Focal or generalized osteolysis of long and flat bones (skull, pelvis, ribs and shoulder-girdle)(14). It may have a “moth-eaten bone” appearance or bone rarefaction, caused by the presence of small lytic areas with
ill-defined margins\(^{(17)}\).
4. Periosteal and subperiosteal reaction, corresponding to areas of thickening of the periosteum due to new bone formation\(^{(6,7,15)}\) (Figure 6).
5. Osteosclerosis, a late and infrequent manifestation\(^{(6)}\).
6. Soft tissue swelling, juxta-articular osteoporosis and joint effusion\(^{(15)}\).

Metaphyseal bands and osteolytic lesions may be observed in up to 70% of cases, whereas osteopenia is seen in up to 25% of patients and fractures in only 10% of children\(^{(16)}\).

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**Figure 3.** Five-year-old boy with bone involvement in leukemia. Anteroposterior radiograph of left ankle shows well-defined radiolucent bands in the metaphyseal region of the distal tibia and fibula (arrows).

**Figure 4.** Bone involvement in leukemia. Anteroposterior radiograph of both knees revealing diffuse osteopenia and metaphyseal radiolucent bands relatively poorly defined in both femurs and tibias (arrows).

**Figure 5.** Twelve-year-old child with bone involvement in leukemia. Lateral radiograph of the thoracic spine depicts diffuse osteopenia and depression of all visible thoracic vertebrae (D4-D10).

**Figure 6.** Bone involvement in leukemia in a 8-year-old child. (a) Anteroposterior radiograph of right knee (a) reveals metaphyseal radiolucent bands in the femur and tibia (arrows). (b) Anteroposterior radiograph of right ankle showing osteolytic area in the lateral border of the distal tibial metaphysis and periosteal reaction of distal shaft in its medial border (arrows).

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**Mediastinum**

Mediastinal involvement typically occurs in ALL\(^{(1)}\). An estimated 15% of these patients present with lymphoma-like clinical features, of which 61% exhibit mediastinal lymph nodes\(^{(18,19)}\). Clinical presentation may vary; it may present with cough, stridor, orthopnea, dyspnea, superior vena cava syndrome or respiratory distress syndrome\(^{(1,3,4)}\).

Radiologically, it corresponds to an anterior mediastinal mass, detectable on plain RX views and confirmed by computed tomography (CT) scans (Figure 7). The differential diagnosis mainly includes lymphoma.
Mammary region

Breast involvement in leukemia is manifested as a lump or breast mass, most often unilateral, which may be present at disease onset or during their evolution. On physical examination, they often appear as well-defined, fast-growing, and sometimes painful tumors (20). On US studies they appear as hypoechoic nodules of well- or ill-defined margins, usually unique (18,19). They are rarely found as multiple bilateral lesions. Additionally, diffuse edema of surrounding tissue and axillary lymph nodes may be observed (20,21).

Testicles

Infiltration of the testes mainly occurs in patients under 20 years of age (21). Leukemia rarely affects this organ primarily; rather, it is often a site of recurrence.

The clinical picture is that of a testicular tumor causing pain, heaviness and/or increased scrotal volume that may be unilateral or bilateral (22,23).

On ultrasonographic studies, an increase in testicular size determined by focal (with multiple nodules) or diffuse involvement, with increased or decreased echogenicity may be observed, being diffuse involvement more frequently encountered (23,24) (Figure 8). In some cases of ALL, there is also infiltration of the epididymis. On color Doppler study an increased blood flow is observed (24).

Conclusions

- Symptoms and signs that suggest an acute leukemia in children are varied and initial manifestations are often nonspecific.
- The imaging study can provide the clinician with valuable information, when first symptoms result from tissue infiltration and involvement of haematological series is discrete and asymptomatic.
- For this reason, the radiologist should be aware of initial radiological manifestations of the disease in children, especially extramedullary involvement, in order to suspect the diagnosis of leukemia in its early stage.
- In particular, the radiologist should consider leukemia in the differential diagnosis of bone pain, visceroelasticity and anterior mediastinal masses in children.

References