

# Acute Leukemia in Children Erroneously Diagnosed as Idiopathic Juvenile Arthritis

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We here present 3 Venezuelan children with acute leukemia, initially diagnosed as idiopathic juvenile arthritis because of the occurrence of pain and joint swelling at the onset of disease. Joint pain was aggravated at night and the arthritis showed a migratory pattern, mainly affecting large joints in an asymmetrical fashion. One patient presented with persistent unilateral sacroiliac pain leading to a wrong diagnosis of spondyloarthritis. The elevation of acute phase reactants, disproportionate to the extent of joint disease, and marked elevation of serum lactate dehydrogenase, as well as characteristic radiological changes allowed the correct diagnosis in all cases. This combination of clinical manifestations, clinical laboratory findings, and joint and bone imaging should prompt the clinician to an early diagnosis of acute leukemia in children with arthritis.

**Key words:** Acute leukemia. Juvenile arthritis. Osteolysis.

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### Leucemia aguda en niños con diagnóstico erróneo de artritis idiopática juvenil

Se presentan 3 niños venezolanos con leucemia aguda cuya enfermedad se inició con dolor e inflamación articular, inicialmente se les diagnosticó artritis idiopática juvenil. El cuadro clínico se caracterizó por artritis migratoria de grandes articulaciones, dolor óseo metafisario de predominio nocturno, aumento de los reactantes de fase aguda desproporcionado para el número de articulaciones afectadas y elevación de la lactatodeshidrogenasa. Un paciente presentó dolor sacroiliaco persistente que condujo al diagnóstico incorrecto de espondiloartritis. Los hallazgos radiológicos

predominantes fueron osteopenia, osteólisis y presencia de bandas radiotransparentes metafisarias. Esta combinación de manifestaciones clínicas, hallazgos de laboratorio y cambios radiológicos debe hacer sospechar una enfermedad mieloproliferativa en niños con inflamación articular.

**Palabras clave:** Leucemia. Artritis juvenil. Osteólisis.

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### Introduction

Myeloproliferative diseases of infancy frequently present with pain and joint swelling, delaying the diagnosis and the start of an adequate treatment when misdiagnosed as diverse forms of juvenile arthritis. The main bone and muscle manifestations associated to malignancy are bone pain, joint pain, muscle pain, and synovial swelling, which can lead to a mistaken diagnosis of juvenile idiopathic arthritis (JIA). We present the case of 3 children from Venezuela with acute leukemia, initially diagnosed as having JIA.

### Clinical Observation

#### Case 1

A 9-year-old female child presented fever, weight loss and migratory elbow, left hip, knees, and ankles arthritis of 1-month duration. A left hip arthrotomy, performed due to the suspicion of septic arthritis, showed non-septic synovial fluid, with negative Gram stain and culture. The patient persisted with fever, pain and limitation of left hip movements, pain on the left sacroiliac joint, and left knee synovitis. Laboratory tests showed leukocytosis, anemia, and elevated platelets. There was also an increase in the levels of lactate dehydrogenase (LDH), quantitative C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) (Table). In light of the sacroiliac joint affection, the diagnosis of juvenile spondyloarthritis was considered. Pelvis x-rays showed multiple lytic lesions and sclerosis of the left iliac bone (Figure, A). A bone gamma scan evidenced an increased uptake of the left sacroiliac region

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**Laboratory Tests**

	Case 1	Case 2	Case 3
Hemoglobin, g/dL	9,7	6,9	8,4
Leukocytes, $\times 10^3/\mu\text{L}$	9,6	3,8	6,9
Platelets, $\times 10^3/\mu\text{L}$	575	135	597
Erythrocyte sedimentation rate, mm/h	100	40	130
Fibrinogen, mg/dL	632	789	541
C-reactive protein, mg/mL	15.3	16.5	20.2
Lactate dehydrogenase, U/mL	303	694	629
Rheumatoid factor	Negative	43 <sup>a</sup>	52 <sup>a</sup>
ANA	Negative	Negative	Positive

<sup>a</sup>Nephelometry, reference values: 20-43 U/mL. Case 1, latex test.

and a computerized tomography revealed a hipodense tumor which occupied the left half of the sacrum and caused periostitis, apoptosis, and bone deformity (Figure, B). A bone marrow biopsy presented hypercellularity and alterations in cell morphology compatible with acute myeloid leukemia (AML). The definitive diagnosis of leukemia was carried out 2 months after the start of clinical manifestations.

In spite of hematologic remission after 6 months of starting chemotherapy with idarubicin, arabinoside C, and etoposide, the sacrum tumor continued growing and limited gait due to an increase in pain and the development of a flexion contracture of the left hip. A new biopsy of the lesion showed a malignant, round cell tumor with little differentiation.

**Case 2**

An 8-year-old male child was hospitalized due to a fever of 38.5 °C, migratory elbow and knee arthritis, synovial effusion and flexion contracture of the left knee of 1 month duration. The child had pain and limitation for the internal rotation of the right hip and right ankle swelling. Laboratory tests showed leukocytosis, anemia, and elevated platelets. One week later he presented leukopenia ( $3.8 \times 10^3/\mu\text{L}$ ), increased ESR ( $>40$  mm/h), CRP (16.5 U/mL), and LDH serum concentration (520 U/mL) (Table). X-rays of the knees showed radiotransparent metaphyseal bands in the distal femur and bilateral tibia. An initial diagnosis of JIA was made. In light of the persistent hematologic alterations, a bone marrow aspirate was performed showing a 95% blast infiltration, confirming the diagnosis of acute lymphoblastic leukemia (ALL) with an L1 morphology. The joint symptoms remitted 1 week

after the start of chemotherapy with prednisone, methotrexate, vincristin, asparaginase, and daunorubicin.

**Case 3**

A 10-year-old male child presented with symmetric arthritis of the knees, ankles, and wrists that had lasted for 2 months. Laboratory tests showed anemia, an increase in the ESR and rheumatoid factor (Table). The diagnosis of systemic JIA was made and treatment with methotrexate 5 mg/week and prednisone 10 mg/day was started, with an improvement of the joint swelling, but recurrence on reduction of prednisone below the stated dose. After 6 months, the child presented a loss of appetite, weight loss, lumbar and bilateral sacroiliac pain and had a pathological complete fracture of the diaphysis of the left femur that led to flexion contracture of the hip of the same side. Physical examination showed multiple submaxillary, cervical,

**Figure.** Image of the pelvis of case 1. A: simple x-ray showing sclerosis and lytic lesions of the left iliac bone. B: tomography of the pelvis that shows a tumor surrounding the iliac bone as well as osteolytic lesions and periostitis.

supraclavicular, and femoral adenopathies, face and eyelid edema and synovitis of the right wrist and knee as well as left ankle. Laboratory tests showed anemia, thrombocytosis, as well as elevated fibrinogen, ESR, LDH, and CRP (Table). Rheumatoid factor remained positive and antinuclear antibodies (ANA) were detected with an intensity of 3+ and a diffuse pattern (Table). The radiologic studies showed severe diffuse osteopenia and multiple lytic lesions of long bones. A guided biopsy of the lytic lesions of the left tibia demonstrated a malignant, round cell tumor, leading to the diagnosis of leukemia or Ewing's sarcoma. A bone marrow aspirate showed lymphoblastic infiltration and the biopsy confirmed the diagnosis of ALL with a L2-L3 morphology. Joint manifestations disappeared completely after 2 weeks of chemotherapy with prednisone, vincristin, asparaginase, and daunorubicine, continuing to this day with hematologic remission.

## Discussion

Acute leukemia's are the most frequent malignant diseases of childhood, representing 30% to 32% of all cancers in children.<sup>1,2</sup> The definitive diagnosis and the start of adequate therapy is frequently delayed when they are mistaken with juvenile arthritis due to a high frequency of acute bone and muscle manifestations as an initial clinical finding.<sup>3-5</sup> The presentation with bone and muscle pain and joint swelling occurs in 10%-62% of cases; synovitis in itself is the less frequent manifestation.<sup>3-6</sup> ALL is the form of acute leukemia in which the rheumatic syndromes are most frequently present.<sup>3,5</sup>

The cases communicated above coincide with the literature with respect to the clinical presentation, with a predominantly migratory pattern, an oligoarticular distribution and a predominant affectation of large joints. One of our children had an infrequent presentation due to sacrum affection and an invasive soft-tissue and osteolytic tumor (Figures, A and B). Two of the 3 cases had fever, one of the most frequent systemic manifestations seen in these patients<sup>3,7</sup> and something common in patients with certain forms of JIA. The girl was initially classified as a juvenile spondyloarthropathy due to sacroiliac pain caused by a soft-tissue tumor in that localization. We have found no reports in the literature of acute leukemia presenting as spondyloarthritis.

The initial clinical presentation with bone and muscle manifestations leads to a delay in the definitive diagnosis and treatment of leukemia in weeks to months<sup>3,7,8</sup>; an average variation of 2 weeks to 18 months in the diagnostic delay has been reported.<sup>3,5</sup> Our cases were initially diagnosed as JIA and leukemia was demonstrated after 1, 2, and 8 months (cases 2, 1, and 3, respectively).

Clinical data which should lead to the suspicion of leukemia are the great intensity of pain and its nocturnal exacerbation, the asymmetric distribution of joint disease, the poor response to non-steroidal anti-inflammatory drugs and the progressive course of the disease.<sup>3,6</sup>

The hematologic profile is of little use as a differential diagnosis tool. Blasts in peripheral blood are not always present during the first months of the disease<sup>7</sup> and the leukocyte count is frequently normal. The association of leucopenia, anemia, and thrombocytopenia with nocturnal pain is highly sensitive (100%) and specific (89%) for the diagnosis of acute leukemia in children.<sup>6</sup> In this report, the leukocyte count was normal in 2 cases and reduced in 1, while anemia, elevated platelets, ESR and LDH were common in the 3 cases (Table). An increase in LDH in children is a reflection of increased cell proliferation<sup>7</sup> and should alert the clinician to the possibility of leukemia because it is an almost universal finding in these forms of malignancy and is typically elevated in ALL,<sup>7,9</sup> making it useful for differentiating between leukemia and JIA.<sup>10</sup> The most frequent radiologic alterations in children with leukemia are osteopenia, radiotransparent or radiolucid metaphyseal bands, periostitis, and sclerosis.<sup>12</sup> All of our cases present osteopenia, metaphyseal bands, and lytic lesions. There were no cases of sacrum infiltration, as was seen in case 1.

Based on this experience we would recommend that the prompt differential diagnosis of ALL be made in a child with pain and recent onset joint inflammation and with the abovementioned laboratory and radiology alterations.

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