Acute Leukemia in Children Erroneously Diagnosed as Idiopathic Juvenile Arthritis

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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 malignity 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 arthrocentesis, 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 predominant were osteopenia, osteolysis and presence of band radiotransparent metaphases. This combination of clinical manifestations, laboratory and changes radiologic should make the clinician to an early diagnosis of acute leukemia in children with arthritis.

Key words: Acute leukemia. Juvenile arthritis. Osteolysis.
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 moths after the start of clinical manifestations.

In spite of hematologic remission after 6 moths 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 (3.8×10^3/µL), increased ESR (>40 mm/h), CRP (16.5 U/mL), and LDH serum concentration (520 U/mL) (Table). X-ray of the knees showed radiotransparent metaphysical 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, vincritin, asparginase, and daunorrubicine.

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 submaxillar, cervical,

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>9.7</td>
<td>6.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Leukocytes, ×10^3/µL</td>
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<td>3.8</td>
<td>6.9</td>
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<tr>
<td>Platelets, ×10^3/µL</td>
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<td>597</td>
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<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
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<td>130</td>
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<td>Fibrinogen, mg/dL</td>
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<td>541</td>
</tr>
<tr>
<td>C-reactive protein, mg/mL</td>
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<td>16.5</td>
<td>20.2</td>
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<tr>
<td>Lactate dehydrogenase, U/mL</td>
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<td>629</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
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<td>43*</td>
<td>52*</td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

*Nephelometry, reference values: 20-43 U/mL. Case 1, latex test.

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, asparginase, 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.\textsuperscript{1,2} 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.\textsuperscript{3,5} The presentation with bone and muscle pain and joint swelling occurs in 10%-62% of cases; synovitis in itself is the less frequent manifestation.\textsuperscript{3,6} ALL is the form of acute leukemia in which the rheumatic syndromes are most frequently present.\textsuperscript{3,5}

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 affection 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\textsuperscript{3,7} and something common in patients with certain forms of JIA. The girl was initially classified as a juvenile spondyloarthropathy due to sacroiliac pain caused as well as elevated fibrinogen, ESR, LDH, and CRP present.\textsuperscript{3,5}

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.\textsuperscript{3,6}

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\textsuperscript{2} 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.\textsuperscript{4} 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\textsuperscript{7} and should alert the clinician to the possibility of leukemia because it is an almost universal finding in these forms of malignity and is typically elevated in ALL,\textsuperscript{7,9} making it useful for differentiating between leukemia and JIA.\textsuperscript{10} The most frequent radiologic alterations in children with leukemia are osteopenia, radiotransparent or radiolucent metaphisal bands, periostitis, and sclerosis.\textsuperscript{12} All of our cases present osteopenia, metaphisal 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.

References
