Childhood Leukemia Presenting as Clinical Arthritis and Chronic Recurrent Multifocal Osteomyelitis (CRMO): Case Report

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Abstract

A previously healthy 5-year-old boy was seen in the rheumatology clinic with a 5-month history of migrating joint discomfort, followed by right knee and left ankle arthritis. He showed no signs of lymphadenopathy, organomegaly, rash, or fever. He could not bear weight and had nocturnal pain that was out of proportion for juvenile idiopathic arthritis. Blood tests revealed no pancytopenia with normal blood film, uric acid, LDH, LFT, and electrolytes. Further evaluations were undertaken in view of his unusual presentation, elevated inflammatory markers, and protracted disease course. An extensive enhancement of nearly all bones was detected on a whole-body MRI, a feature thought to be consistent with chronic recurrent multifocal osteomyelitis (CRMO). However, a bone biopsy followed by marrow aspiration confirmed a diagnosis of pre-B-cell Leukemia. The importance of considering childhood malignancies as JIA and CRMO-mimickers, even in the absence of typical neoplasm symptoms, is highlighted by this interesting case.

Keywords: Childhood; Musculoskeletal Complaints; Acute Lymphoblastic Leukemia; Juvenile Idiopathic Arthritis; Chronic Recurrent Multifocal Osteomyelitis.

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in childhood, accounting for approximately one-third of all pediatric cancers.(1) Typical clinical presentations often include symptoms such as pallor, fatigue, fever, easy bruising and bleeding, and bone pain, among others.(2) This is further supported clinically by the presence of cytopenia, organomegaly, and lymphadenopathy. Although bone pain has been reported to occur in around 30–40% of patients, clinical arthritis as the sole presenting feature of ALL in childhood is a rare occurrence that warrants further investigation.(3–5)

Case Report

We hereby present a 5-year-old boy who was referred to Rheumatology with a 5-month history of migratory joint pain to rule out juvenile idiopathic arthritis (JIA).

Symptoms started as non-specific pain in the knees, ankles, shoulders, and back with no apparent swelling. He had no history of fever, morning stiffness, or preceding illness. Joint pain was worse at night, which, with time, rendered him immobile. He was still able to use his upper limbs freely. He had occasional vomiting and a loss of appetite, but no weight loss. The review of systems was unremarkable.
On assessment, the child was in a wheelchair. Biometric and developmental assessments were appropriate for age. He had no pallor, rashes, or lymphadenopathy. His CVS, chest, and abdominal examinations were all normal. His left knee was significantly swollen and tender. The right ankle demonstrated limited flexion. He had significant bilateral leg muscle atrophy but normal power and reflexes. His gait and Gower’s sign could not be assessed.

He was admitted for pain control and further workup. The labs were as shown in Table 1. The CXR and ultrasound abdomen were normal. X-rays of the left knee (Figure 1) showed heterogeneous luencies with diffuse erosions. Whole-body MRI revealed multifocal heterogeneous areas of T2 hyperintensity affecting almost all bones, including the sternum, pelvis, and phalanges of the hands and feet. A small effusion of the left knee was present. Features were in keeping with chronic recurrent multifocal osteomyelitis (CRMO).

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Results</th>
<th>Laboratory Tests</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>11.8 (11.5 - 15.5 g/dL)</td>
<td>LFT</td>
<td>Normal</td>
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<tr>
<td>platelets</td>
<td>433 (150 – 450 109/L)</td>
<td>TFT</td>
<td>Normal</td>
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<tr>
<td>WBC</td>
<td>5.6 (4.5 - 14.5 109/L)</td>
<td>Mg</td>
<td>Normal</td>
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<tr>
<td>ANC</td>
<td>2.1 (1.4 - 9.0 109/L)</td>
<td>Uric acid</td>
<td>Normal</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>3.0 (1.9 - 9.8 109/L)</td>
<td>LDH</td>
<td>Normal</td>
</tr>
<tr>
<td>Urea &amp; electrolytes</td>
<td>Normal</td>
<td>CK</td>
<td>Normal</td>
</tr>
<tr>
<td>CRP</td>
<td>21 (&lt;1)</td>
<td>Urine PCR</td>
<td>Normal</td>
</tr>
<tr>
<td>ESR</td>
<td>60 (&lt;10)</td>
<td>ANA</td>
<td>+ve 1:80 (low titre)</td>
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<td>all negative.</td>
<td>ENA</td>
<td>negative</td>
</tr>
</tbody>
</table>


**Figure 1:** X-ray of left knee showing heterogeneous luencies of the distal femoral metaphysis, proximal tibial metaphysis, and proximal fibular metaphysis with diffuse erosions.
Whole Body MRI showing multifocal heterogeneous areas of T2 hyperintensity affecting mainly the long bones [epiphysis, metaphysis and diaphysis with affinity to the metaphysis]. Other cuts showed changes in the humeral, radial, ulnar, carpal, metacarpal, femurs, tibias, fibulas, tarsal, sternum, scapulae, clavicles, multiple spinal processes, posterior-superior iliac spines, iliac crests, and phalanges of the hands and feet.

There are periosteal elevation and surrounding soft tissue edema at the distal left femur and proximal left tibia. There is focal thinning of the cortex of the tibia at this region. Small joint effusion of the left knee. Brain parenchyma is unremarkable.

A left femur bone biopsy showed replacement of the marrow by sheets of immature blasts. Blood film, bone marrow aspirate, and flow cytometry showed 66% blasts and features consistent with precursor B-cell acute lymphoblastic leukemia with a common B-immunophenotype (WHO 2017). The child was started on UKALL 2011-Regimen A and he continues to show a favorable response at the time of writing of this report.

Discussion

Arthritis, characterized by joint pain, swelling, and limitation of motion, is commonly associated with various rheumatic diseases. However, it can also be seen in metabolic, genetic, orthopedic, and oncological conditions. The number of affected joints, the duration and pattern of symptoms, their relationship to daily activity and stiffness, and prior infections or triggering factors are all crucial information in determining the etiology of arthritis.

Nonetheless, the development of arthritis-like symptoms as an initial manifestation of ALL in children raises important clinical and diagnostic challenges. Understanding the mechanisms underlying this unusual presentation is crucial for accurate and timely diagnosis as well as appropriate management. While the pathogenesis of arthritis in ALL remains poorly understood, it has been proposed that leukemic cells infiltrate the synovium, causing joint inflammation and subsequent arthritis-like symptoms.(6,7)

Juvenile Idiopathic Arthritis (JIA) is the most common chronic autoimmune disorder in children under the age of 16.(8) Unfortunately, ALL arthritis-like symptoms can be misinterpreted as JIA if they present with multiple joint involvement for more than 6 weeks, ANA positivity, and no cell line abnormalities, delaying the ultimate diagnosis and treatment.(3) In addition, corticosteroids, a treatment used for arthritis, can further mask the clinical and laboratory findings of malignancies.
Our patient presented with a significantly tender knee, an inability to bear weight, disturbed sleep, and repeated vomiting, which, when put together, were not in favor of JIA, triggering the search for other differential diagnoses. He had a low positive antinuclear antibody (ANA) titer of 1:80 with negative dsDNA and extranuclear antibodies (ENA), making the possibility of connective tissue disorders less likely. Due to its non-specificity and the possibility that it may also be present in non-rheumatic disorders such as infections and malignancies, ANA should not be used to distinguish between these conditions. (9)

This case was unique as the MRI showed features in keeping with chronic recurrent multifocal osteomyelitis (CRMO), which is a rare autoinflammatory bone disorder characterized by recurrent episodes of bone inflammation, predominantly affecting the clavicle, sternum, vertebrae, and metaphysis of long bones. (10) CRMO of small bones appears to be less common. (11) The exact cause of CRMO is not yet well understood but is believed to be due to a dysregulated immune response. (10) Although it has a typical radiological appearance characterized by osteolysis, sclerosis, and hyperostosis, these are not distinctive enough to make a definitive diagnosis, adding to the challenges of diagnosing CRMO. (12,13) Its variable presentation, close resemblance to other musculoskeletal disorders, and lack of specific diagnostic biomarkers pose challenges in distinguishing it from many similar-presenting conditions. The misinterpretation of MRI findings and biopsy results can further contribute to this delay. (14,15)

Our patient’s long-standing intermittent bone symptoms, an MRI finding with multifocal involvement, and raised inflammatory markers, if applied, can fulfill the three proposed sets of criteria. (16,17) However, his extreme pain and widespread bone marrow enhancement of even small bones were of major concern, necessitating the need for a bone biopsy. Although no blasts were detected peripherally, the biopsy confirmed the diagnosis of ALL. A lesson learned here is not to exclude malignancies in view of a normal peripheral blood smear and the absence of typical neoplasm symptoms. This is further supported by several previous studies reporting the absence of blasts in ALL patients presenting with MSK complaints. (18,19)

**Conclusion**

A high level of clinical suspicion and a comprehensive diagnostic approach are crucial when encountering a patient with atypical joint symptoms such as intense pain, nocturnal symptoms, and the absence of morning stiffness. This case was presented to emphasize the rarity and importance of considering clinical arthritis as one of the only presenting features of childhood malignancies, even in the absence of cytopenia, fever, lymphadenopathy, and hepatosplenomegaly.

**Conflict of interest**

We declare no conflict of interest. The case has not been published and is not under consideration for publication in any other journal.

**Acknowledgements**

We are grateful to our patient and his parents for their participation. Consent was taken from his mother.

**References**


