**Prolonged Musculoskeletal Symptoms, Bone Lesions on MRI and Patchy Bone Marrow Involvement in 2 Adolescents with Hypodiploid ALL: Case Series and Review of Literature**

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**Abstract**

Acute Lymphoblastic Leukemia (ALL) is typically diagnosed with an abnormal CBC and blasts on peripheral blood smear and confirmed with peripheral blood or bone marrow flow cytometry. However, this is not always the case, sometimes the diagnosis is guided by other diagnostic tools such as imaging. This case series presents 2 patients with normal white blood cell count, absence of peripheral blasts on the blood smear, bone lesions on Magnetic Resonance Imaging (MRI), patchy involvement of the bone marrow, and paucity of bone marrow samples, which later were diagnosed with hypodiploid acute lymphoblastic leukemia.

MRI can be a useful tool in patients presenting with prolonged musculoskeletal symptoms with underlying hypodiploid ALL, to help direct early bone marrow examination.

**Keywords:** Hypodiploid; Leukemia; Musculoskeletal; MRI.
Case presentation

Case 1: Is a 16-year-old male with no significant past medical history, with a 3-month history of sharp bilateral knee pain, causing him to limp, and no improvement with NSAIDs. Associated symptoms included frontal throbbing headache, right jaw pain, lower extremity pain, chest pain, and left peripheral facial paralysis, initially assumed to be Bell’s palsy, with no prescribed treatment.

One month prior to admission, he developed a fever and was diagnosed with pneumonia at a local hospital. He also had night sweats, left wrist and lumbar pain, fatigue, and weight loss (40 pounds in 3 months). Due to progressive symptoms, he came to our hospital in July 2021. Vital signs were within normal limits. On physical exam, he was pale, with no hepatosplenomegaly or lymphadenopathy, and with limited range of motion on the left upperextremity and back due to pain. No signs of arthritis onexam.

X-rays on sacroiliac joints and wrist joints were normal. Labs revealed increased acute phase reactants (ESR normal above 100 mm/h, CRP 15.3 mg/dl), LDH 1073 U/L, uric acid 3.5 mg/dl, Ca 9.9 mg/dl, anemia (Hb 8.9 gm/dl, Hematocrit 26.8%, MCV 85.9 fl., MCH 28.5 pg), normal WBC and platelets (WBC 9.2 th/ul, platelets 209 th/ul) and blood smear showing normochromic, normocytic anemia, with no WBC and platelet abnormalities. Rheumatology was consulted. A spine and pelvic MRI were requested, showing diffuse heterogeneous T1 hypointense and T2 hyperintense signal in the bone marrow, reported to be most consistent with leukemia (Figure 1).

Initial bone marrow evaluation provided sample enough for morphology and core biopsies alone, which were consistent with B-ALL, with >95% cellularity and 50% blasts (CD20+, CD79a+, CD43 weak +, CD45 partial +, TdT+, CD10+ on immune stains). Bone marrow aspiration was repeated due to the need for more samples to complete evaluation and cytogenetics. That sample showed a markedly diluted marrow with 0.5% blast cells by flow cytometry, presumed due to hemodilution.

Bilateral bone marrow aspirate and biopsy were repeated the following day. Both aspirate showed hypocellularity, and multiparameter flow cytometry showed a small population of atypical B cells consistent with lymphoblasts (1%). Core biopsies showed extensive necrosis and focal positivity for CD43 and TdT. Discordance in the bone marrow findings was presumed to be due to patchy involvement. Cytogenetics was significant for a hypodiploid clone with 39 chromosomes. Those findings indicated a hypodiploid B cell clone with CD20, CD79a, CD43 weak +, CD45 partial +, TdT+, CD10+ on immune stains. Given that, the clonal cell population had yet unknown clinical significance, the patient was discharged and followed with serial CBC’s. Eight weeks later, the CBC showed 11% of peripheral blasts on the manual differential. The patient’s hip pain was significantly worse, and she was admitted for pain management and bone marrow evaluation.

Bone marrow evaluation provided aspirate sample enough for flow cytometry and core biopsy alone with 45% blasts on flow cytometry, positive for CD45, CD10, CD19, CD20, CD22 (Partial positive on 62% of blasts), CD38, and HLA-DR, confirming B-cell ALL. Biopsy showed >95% cellularity with marrow completely replaced with blast. Bone marrow evaluation had to be repeated multiple times by 2 different experienced oncologists and one orthopedic surgeon due to difficulty obtaining enough samples on aspirate. The core biopsy was sent for cytogenetic and demonstrated monosomy 4, 12 and 17. Given the diagnosis of hypodiploidy, she was classified as Very High Risk and started 4-drug induction. Bone marrow aspirate done at End of Induction bone marrow evaluation was performed without difficulty on Day 29, with flow cytometry showing no evidence of residual B lymphoblastic leukemia.

Summary of key findings regarding presentation and diagnosis on both cases are mentioned in Table 1.

Case 2: Is a 16-year-old female with no significant medical history, who presented with a one-month history of right hip pain. Initially, the pain was intermittent, referred to as a click sensation, and became throbbing afterward. She visited an outside clinic, where she was prescribed symptomatic treatment. After 2 weeks, the pain became progressively worse, with no improvement with NSAIDS or rest.

Due to the persistence of symptoms, she presented to our institution. On arrival, a physical exam showed vital signs within normal limits, right hip pain with external rotation, tenderness on palpation of right hip, and intact range of motion. No hepa-tosplenomegaly or lymphadenopathies were noted. Hip x-ray was normal. She was seen by the orthopedic surgeon; hip MRI showed innumerable abnormal T1 hypointense and T2/STIR hyperintense enhancing lesions involving the pelvic bones, proximal femurs, and L5 vertebral body reported as likely metastases (Figure 2).

A Neck/Chest/Abdomen and Pelvis CT were performed, with no definite space-occupying lesion identified. Laboratory studies on admission were normal: WBC (7.0 th/ul) with no evidence of blasts on manual differential, Hemoglobin 11.9 gm/dl; MCV 92.0 fl; Platelet 347 th/ul; Calcium 8.3 mg/dl (9.3 when corrected for hypoalbuminemia); Albumin 2.8 g/dl; Uric Acid 3.1 mg/dl and LDH 117 U/L.

On the second day of admission, due to suspected metastatic diagnosis, an open right iliac bone biopsy with bone marrow aspiration and biopsy were performed by orthopedic surgery. Bone biopsy measuring 3.5x2x1.9 cm showed patchy involvement with focal areas showing diffuse blasts CD20 and CD79a positive, TdT weakly positive, mixed with areas of residual marrow present. Bone marrow aspirate immunophenotyping showed a small population (3.8%) of variably sized cells positive for CD10, CD19, and CD20. B cell FISH was positive for monosomy 4 and 17 in 10% of cells, and one copy of ETV6. Microarray analysis showed multiple chromosomal losses (chromosomes 2, 3, 4, 7, 12, 13, 15, 16, 17) congruent with B cell FISH findings. Those findings indicated a hypodiploid B cell clone with 37 chromosomes. Given that, the clonal cell population had yet unknown clinical significance, the patient was discharged and followed with serial CBC’s. Eight weeks later, the CBC showed 11% of peripheral blasts on the manual differential. The patient’s hip pain was significantly worse, and she was admitted for pain management and bone marrow evaluation.

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by experienced oncologists on different occasions, and including one attempt in the femur by an orthopedic surgeon in patient number 2. This forced a diagnosis based on core biopsies, and comprehensive risk stratification could not be completed.

Hypodiploid leukemia is an infrequent subtype in acute lymphoblastic leukemia in children and adults, and a marker of poor prognosis [4]. We can divide this category into high hypodiploid (40-45 chromosomes), low hypodiploid (31-39 chromosomes), and near haploid (24-30 chromosomes) [4,5]. Low hypodiploid has been reported in 0.5% of ALL in children, and 3-4% in adult ALL, and near haploid in 0.5% of childhood ALL, and has not been reported in adults [4]. Both of our patients fit into the low hypodiploid category.

Near haploid and low hypodiploid, have different target mutations. While near haploid leukemias frequently have mutations compromising the function of RAS pathway and tyrosine kinase receptors (like NF1, histone modifiers, CREBBP, among others), in low hypodiploid ALL the most frequent mutation involves TP53, both in childhood (most likely constitutional) and adults (usually somatic) [4-6]. Those mutations were not found in our patients, although samples were scarce.

Children with low hypodiploid ALL tend to be older than near haploid ALL (median age 11.5 years vs the median of 5 years old) [4]. The 2 patients presented in this article were older than the median age for the low hypodiploid group. Hypodiploid leukemia implies worse EFS and OS, with a reported 5 to 8-year EFS rate of 25-40% for near haploid ALL and 30-50% for low hypodiploid ALL, and OS of 35-50% for hypodiploid ALL [4]. Our patients continue chemotherapy, with negative MRD at the end of induction.

Usually, diagnosis of a hematologic malignancy can be made based on localized and generalized symptoms, abnormalities in blood tests, and results on the analysis of tissue biopsy or marrow aspirate [7]. Patients can present with fever, asthenia, pallor, lymphadenopathies, hepatosplenomegaly, and usual laboratory findings include anemia, thrombocytopenia, and neutropenia, among other abnormalities [1]. However, in up to 22 to 38% of cases, children with acute leukemia can have non-specific musculoskeletal complaints [7]. In our case series, bone pain and arthralgias were the most significant symptoms. It can

Discussion

Acute Lymphoblastic Leukemia (ALL) is the most prevalent cancer among children and adolescents in the United States, with a peak incidence between 2 and 5 years of age and represents 25-30% of all childhood cancers [1]. Overall incidence of pediatric ALL during 2001-2014 was 34.0 cases per 1 million persons [2].

Bone marrow evaluation, with morphology analysis, is the gold standard in diagnosing childhood leukemia. Flow cytometry helps identify the immunophenotypic characteristics of the blasts, not only at diagnosis but also during treatment, to assess MRD [3], a valuable tool to monitor response. Peripheral blood flow cytometry has become useful as well in the detection of peripheral blasts, with the ability to identify a clonal population as low as 0.04% [3].

Besides the prolonged symptomatology (months), our patients shared the diagnosis of hypodiploid acute lymphoblastic leukemia, and the paucity of bone marrow samples due to scarce material obtained after biopsy, despite multiple attempts

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<th>Table 1: Key points in case presentation.</th>
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<td><strong>Case 1</strong></td>
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Figure & Case 2: Hip MRI showing abnormal T1 hypointense and T2/STIR hyperintense enhancing lesions involving the pelvic bones, proximal femurs, and L5 vertebral body.

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be caused by infiltration of leukemic cells in the periosteum, expansion of the marrow cavity by such cells, or bone infarction [1]. Osteoarthralgia in patients with acute leukemia tends to be migratory, asymmetric, and the limited inflammatory findings don’t usually correlate with their severe pain [8]. Our patients presented such symptoms for months before admission, with a delay in diagnosis mostly due to the normal initial laboratory results and benign findings on physical exam.

In children, especially younger ones, an incomplete history, and physical examination can interfere with a correct clinical assessment. In those cases, the progressively increased use of MRI to characterize musculoskeletal symptoms can lead to the occasional incidental detection of abnormal marrow signals that can assist and guide the diagnosis of hematologic malignancy [7]. For both of our patients, MRI was done looking for a local cause for the pain, and the bone infiltration was an incidental finding.

The bone marrow can be affected by multiple disorders, which can be categorized as secondary to hyperplasia, infiltration or depletion of the bone marrow, fibrosis, and deposition of metabolic products [9].

Published literature describes leukemia as a cause for a diffuse or uniform pattern of marrow replacement. This pattern has been called by Ruzal-Shapiro et al. a “flip-flop” in signal intensities between uniform T1 hypointensity and T2 hyperintensity, due to the infiltration of the bone marrow by leukemic blasts, which cause displacement of adipose tissue [7,10]. In rare occasions, these altered signals can be seen in the early stages of the disease, when laboratory abnormalities are still not present [7]. With the cases described previously, MRI findings were present with a normal WBC count and no peripheral blasts. In those cases, it was the abnormal imaging that guided the need to obtain bone marrow samples.

**Conclusion**

This case series describes patients with the diagnosis of hypodiploid acute lymphoblastic leukemia, who presented initially with significant and prolonged bone and articular pain, despite having a normal WBC count and no blasts in peripheral blood, bone lesions in MRI, which ultimately guided the need for bone marrow evaluation. It is important to note that in such patients with persistent musculoskeletal pain and no other abnormal findings, MRI can contribute to the diagnosis. Another key point is to consider the possibility of patchy involvement of the bone marrow in cases of persistence of symptoms and imaging, with negative bone marrow findings. In such cases, it is appropriate to repeat bone marrow evaluation to avoid missing an early diagnosis of malignancy.

**References**