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AUNUSUAL CASE OF ACUTE MYELOID LEUKEMIA PRESENTING AS PYREXIA OF UNKNOWN ORIGIN WITH DIFFUSE INFILTRATIVE BONE LESIONS

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INTRODUCTION

Acute myeloid leukemia (AML) is a malignant neoplasm of hematopoietic stem cells, primarily affecting adults (median age around 65–68 years)[1]. It usually presents with signs of bone marrow failure – anemia (pallor, fatigue), thrombocytopenia (bleeding, petechiae), and neutropenia (infections, fever)[2]. Lymphadenopathy or organomegaly can occur, but overt skeletal symptoms are uncommon. AML only rarely manifests with bone pain or radiologic bone lesions at presentation. We describe an unusual case of an 18-year-old male who presented with prolonged fever (pyrexia of unknown origin) and severe multifocal bone pain, ultimately diagnosed as AML with infiltrative osteolytic bone lesions. This report discusses the rarity of bone lesions in AML, treatment modalities, and key takeaways from this case, with references to recent literature.

Case Presentation

An 18-year-old male, with no known comorbidities, presented to the hospital with a history of intermittent high grade fever for 4 weeks associated with chills, generalized myalgia and multiple joint pain. He reported multiple joint pains involving both shoulders, left arm, lower back, bilateral hips, and the anterior chest wall over the sternum. There was a history of progressive weight loss of approximately 6 kg over the past month and restriction of left shoulder movements for the past month. He denied any history of cough, loose stools, bleeding manifestations or rashes. There was no history of exposure to pets or wild animals, recent travel, prior hospitalization, intravenous drug use, radiation exposure, or consumption of native medicines.

On examination, the patient was conscious and oriented. He was febrile (100 °F) with a blood pressure of 100/60 mmHg, pulse rate of 100 beats/minute, respiratory rate of 18 breaths/minute, and oxygen saturation of 98% on room air.Further examination revealed marked pallor. Multiple firm, non-matted, non-tender lymph nodes were palpable nodes in the left posterior triangle and the left axilla.Cardiovascular, respiratory, and abdominal examinations were unremarkable. Musculoskeletal assessment showed tenderness over both shoulders, bilateral anterior superior iliac spines, lower sternum.

Initial complete blood count revealed pancytopenia with a hemoglobin level of 8.8 g/dL, total RBC count of 2.96 million/cu.mm, platelet count was markedly reduced at 0.42×10^5/cu.mm and total leukocyte count was 3,730/cu.mm. Further laboratorical evaluation revealed elevated inflammatory markers with C-reactive protein (CRP) 34.8 mg/L, erythrocyte sedimentation rate (ESR) 50 mm/hr and markedly elevated Serum ferritin at 885

ng/mL, a corrected reticulocyte count of 0.2%, negative Viral serology (HIV, HBsAg, HCV). Blood and urine cultures yielded no growth.Echocardiography and CT imaging of the thorax and abdomen revealed no significant abnormalities. Peripheral smear (Figure 1)demonstrated 54% circulating blasts. With high suspicion of hematological malignany, bone marrow aspiration(figure 2) and trephine biopsy from the posterior iliac crest was done , which showed mild hypercellularity with suppressed erythropoiesis and megakaryopoiesis and a blast-predominant myeloid series (blasts 92%; myeloid-to-erythroid ratio of 20:1), consistent with acute myeloid leukemia.

Flow cytometry demonstrated myeloid lineage blasts positive for MPO, CD13, CD15, CD117, HLA-DR. Mature myeloid, monocytic and erythroid markers were negative. However aberrant expression of surface CD3, CD41, and CD71 was noted. The findings were consistent with Acute Myeloid Leukemia with minimal maturation. MRI of the left shoulder (Figure 3) demonstrated diffuse infiltrative lesions of left humerus and scapula.

The patient was initiated on induction chemotherapy with two cycles of cytarabine and daunorubicin (7+3 regimen), followed by two cycles of consolidation therapy with intermediate-dose cytarabine (IDAC).Following day 17 of the second IDAC cycle, a repeat peripheral smear demonstrated 30% circulating blasts, indicative of early relapse. Salvage chemotherapy with azacitidine and venetoclax was commenced.During this period, the patient developed persistent pancytopenia, requiring multiple transfusions, including 8 units of single-donor platelets (SDP), 12 units of random-donor platelets (RDP), and 4 units of packed red blood cells (PRBCs). He also experienced severe, diffuse bone pain necessitating opioid analgesia (morphine, methadone) and ketamine syrup.By day 35 from the second IDAC cycle, peripheral smear revealed 96% blast cells, confirming disease progression despite salvage therapy. Given the refractory nature of the leukemia and progressive decline in clinical status, the patient was transitioned to hospice care. He eventually succumbed to his illness.

DISCUSSION

Diagnosing an unusual AML presentation required thorough immunophenotyping and tissue analysis. The flow cytometry, while confirming AML, did not neatly fit a single FAB category – a reminder that some AML cases (especially minimally differentiated AML or those with mixed phenotypes) can be challenging to classify by immunophenotype alone. The presence of extramedullary bone lesions in an AML patient suggests an aggressive biology often seen in certain subtypes (e.g. those with core-binding factor mutations or monocytic differentiation).

Initially, the multifocal bone lesions and lymphadenopathy in our patient raised concern for lymphoma or metastatic solid cancer. Indeed, extramedullary myeloid tumors (myeloid sarcomas) are often misdiagnosed as lymphoma if immunohistochemistry panels are incomplete[2]. In the literature, myeloid sarcoma (also called granulocytic sarcoma or chloroma) is defined as a tumor mass of myeloblasts outside the marrow. It can occur de novo without overt leukemia or concurrently with AML. Adequate panels of myeloid markers (MPO, CD117, CD68, etc.) on a biopsy are crucial to confirm a myeloid sarcoma and avoid a misdiagnosis. In our patient, an MRI of the shoulder showed diffuse marrow signal changes in the humerus and scapula, and a bone marrow biopsy confirmed extensive leukemic infiltration.

Bone involvement with osteolytic lesions is an exceedingly rare manifestation of AML. Extramedullary disease in general (myeloid sarcoma) is seen in a minority of AML patients – incidence ranges from ~0.8% to 10% in different studies[2]. Common sites for myeloid sarcomas include skin, lymph nodes, the orbit, CNS, and soft tissues, while primary bone lesions are infrequent. Osteolytic lesions (areas of bone destruction on imaging) are a hallmark of multiple myeloma or metastatic solid tumors, but are seldom reported in adults with AML[3]. A recent 2024 case report highlighted a 66-year-old AML patient who presented with multiple osteolytic bone lesions and a pathological fracture[2]. That patient's disease was initially mistaken for metastatic cancer, illustrating how unexpected such a presentation is. In our 18-year-old patient, the combination of persistent fever, pancytopenia, and severe bone pain with lytic-appearing lesions on MRI ultimately led to a bone marrow examination that diagnosed AML.

Documented cases of AML with skeletal lesions are extremely scarce. One case report described a 17-year-old boy with acute erythroid leukemia (AML M6) who presented with an osteolytic humeral lesion[4]. Extramedullary involvement is generally very rare in AML M6, and that was reportedly the first ever case of AML M6 with a skeletal presentation[4]. Another report noted an AML M7 (megakaryoblastic leukemia) patient whose bone lesion biopsy showed a myeloid tumor with megakaryocytic differentiation[5]. These examples underscore that virtually any AML subtype *could* present with bone lesions, but the overall prevalence is extremely low. In our patient's age group (adolescent/young adult), ALL (acute lymphoblastic leukemia) is more often associated with bone pain or lesions than AML – pediatric studies in ALL show osteolytic lesions in ~13% of cases. For adult AML, the prevalence of bone infiltrative lesions is not well established, but only isolated case

reports exist. In summary, AML presenting primarily with bone lesions is a medical rarity, which makes recognition and diagnosis challenging. Clinicians should keep AML in the differential diagnosis of unexplained osteolytic lesions with cytopenias, as delayed diagnosis can occur due to the atypical presentation.

The cornerstone of AML treatment for fit patients is intensive chemotherapy to induce remission. For decades, the standard induction regimen has been the so-called "7+3" combination of cytarabine (7 days continuous infusion) plus an anthracycline (e.g. daunorubicin for 3 days) [6]. This regimen achieves complete remission (CR) in roughly 60–80% of younger adults and 40–60% of older adults, depending on risk factors[7]. Our patient, being 18 years old and otherwise healthy, was started on intensive induction chemotherapy according to guidelines (likely a 7+3 protocol). The goal of induction is to rapidly clear leukemic blasts and restore normal marrow function (achieve CR) [6]. In this case, after induction, the blast percentage in peripheral blood fell to about 30%, indicating a partial response but not a full remission. Standard practice would be to proceed with a second induction (re-induction) or move to an early intensification if residual disease persists. However, our patient's condition deteriorated quickly, and standard consolidation therapy could not be effectively delivered.Post-remission therapy in AML is essential to prevent relapse. If a CR is achieved, patients typically receive consolidation chemotherapy (often high-dose cytarabine-based courses) and/or proceed to allogeneic hematopoietic stem cell transplantation (HSCT) if indicated [6]. Transplant is considered for patients with high-risk features or those who do not achieve molecular remission, as it offers the highest chance of cure in adverse-risk AML. In our patient's case, a transplant was not feasible since a complete remission was never attained and the disease was refractory. Throughout treatment, supportive care is crucial – transfusions of red cells and platelets (as our patient required frequently), prophylactic antimicrobials, and vigilant infection control are standard supportive measures. Pain management was also a significant issue in this case due to bone involvement; despite high-dose analgesics, his bone pain was difficult to control. Notably, there are reports of using localized radiation therapy to palliate severe bone pain or spinal cord compression from myeloid sarcomas. Some prior cases of AML with bone lesions achieved partial relief of focal bone pain with local radiotherapy [2]. In practice, systemic chemotherapy is the mainstay to treat extramedullary leukemia, but radiation can be added for symptom control in select situations. Venetoclax combined with a hypomethylating agent is a newer protocol that has become standard for elderly or unfit patients with AML [6] , and is also showing activity in refractory cases. Unfortunately, despite this salvage regimen, our patient's leukemia proliferated (96% blasts on repeat smear), reflecting highly resistant disease. Other emerging treatments include oral azacitidine for maintenance, hedgehog pathway inhibitors (glasdegib), and the very recently approved menin inhibitor (revumenib) for KMT2A-rearranged or NPM1-mutated AML. While these advances are promising, the backbone of initial therapy remains chemotherapy for most patients, and timely referral to clinical trials or transplant is advised for aggressive cases. In summary, the optimal management of AML involves rapid induction therapy to achieve remission, appropriate use of consolidation (chemotherapy or transplant), and incorporation of novel agents based on the leukemia's molecular profile. In cases of extramedullary AML, the treatment principles are similar – systemic chemotherapy is required to control the disease, with local measures (like radiotherapy or surgery) reserved for emergent complications or refractory localized pain.

FINAL CONCLUSION

This case highlights an **atypical presentation of acute myeloid leukemia with minimal maturation** in an adolescent, manifesting with **diffuse bone lesions** involving multiple skeletal segments, an uncommon finding in adult AML. Flow cytometric interpretation was challenging due to **aberrant multi-lineage antigen expression**, which can complicate lineage assignment and risk assessment. The disease followed an **aggressive clinical course**, with early relapse after standard induction and consolidation therapy, rapid progression despite salvage treatment, and refractory disease culminating in death within months of diagnosis. Recognition of such unusual skeletal manifestations and complex immunophenotypic patterns is important, as they may herald an underlying aggressive disease biology, warranting early risk-adapted and potentially intensified therapeutic strategies.

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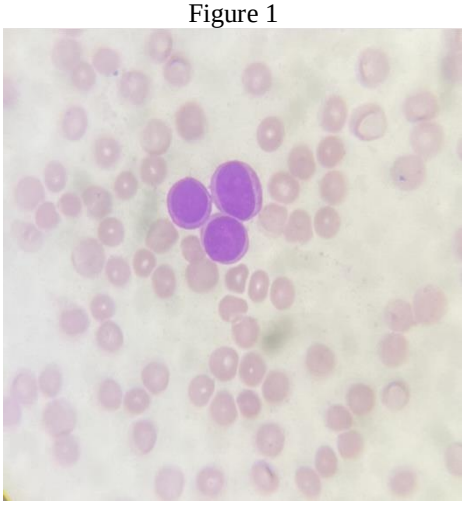
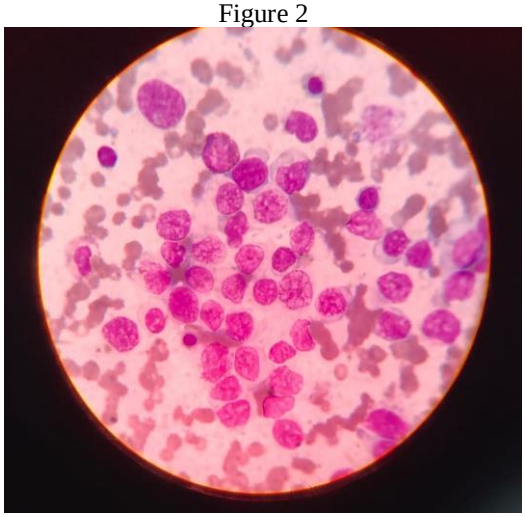
Figure 1



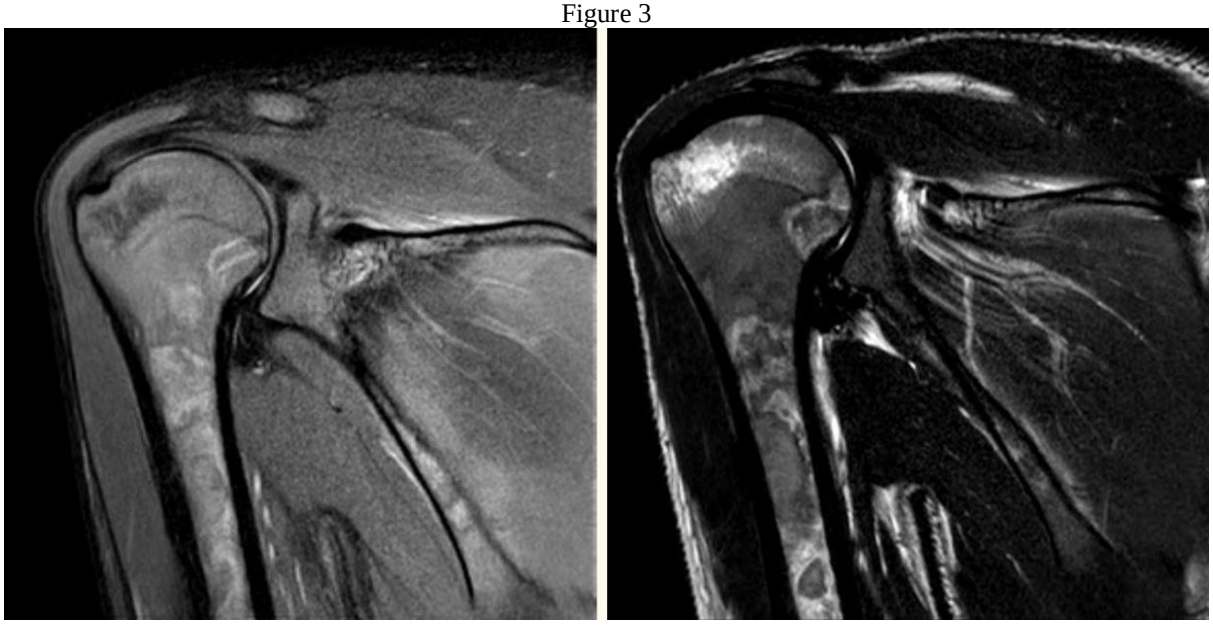
Peripheral smear demonstrated 54% circulating blasts, with occasional myelocytes (2%) and band forms (10%) with no other significant abnormalities

Figure 2



Bone marrow aspiration examination - Increased preponderance of blasts.MYELOID: ERYTHROID RATIO:20:1. Erythroid cells-5%,**Blasts-92%**,Neutrophils-1%,Lymphocytes-2%. Diminished erythropoiesis and megakaryopoiesis

Figure 3



MRI of left shoulder - Coronal T1-weighted (left) MRI of the left shoulder demonstrating hypo- to isointense signal and Coronal T2-weighted/STIR MRI of the left shoulder demonstrating heterogeneously hyperintense marrow signal changes involving the epiphysis, metaphysis, and diaphysis consistent with diffuse leukemic marrow infiltration.