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CASE REPORT

Acute Leukaemia of Ambiguous Lineage Presenting as a Focal Bone Lesion: a Case Report

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INTRODUCTION

Acute leukaemia is the most common childhood malignancy. Almost all cases are classified as acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML). Acute leukaemia of ambiguous lineage (ALAL) is a rare form of acute leukaemia that cannot be classified by a single lineage.[1] Like other acute leukaemias, ALAL typically presents with nonspecific symptoms such as fatigue, fever, or bleeding.[2] Although presentation with musculoskeletal symptoms such as bone pain is not uncommon in acute leukaemia, a focal pattern of bone involvement at presentation is rarely observed and has not been described in children with ALAL. We describe the case of a 16-month-old girl with ALAL who presented with a focal destructive bone lesion.

CASE REPORT

A 16-month-old girl was referred to our oncology unit with a 3-week history of progressive pain, irritability and inability to bear weight on her left lower limb. She was a twin born at 34 weeks' gestation from an in vitro fertilisation pregnancy and was well prior to presentation.

A radiograph of the left femur (not shown) revealed a permeative lytic lesion in the left distal femoral metaphysis. Lower limb computed tomography (CT) showed a destructive lesion, with a small soft tissue mass, suggestive of a primary bone tumour, Langerhans cell histiocytosis, or a metastasis (Figure 1). Magnetic resonance imaging (MRI) of the thighs showed numerous other focal bone lesions, all asymptomatic (Figure 2), and CT of the chest and abdomen showed no evidence of lymph node enlargement, organomegaly or soft tissue mass. Initial blood investigations and urinary catecholamines were normal. The femoral lesion was biopsied, revealing a largely necrotic undifferentiated neoplasm with focal areas of viable tissue and large round blue cells. The viable cells were positive for CD99, CD43, CD34, CD117, vimentin and CD56, and negative for lymphoid and other solid tumour markers on immunohistochemical staining.

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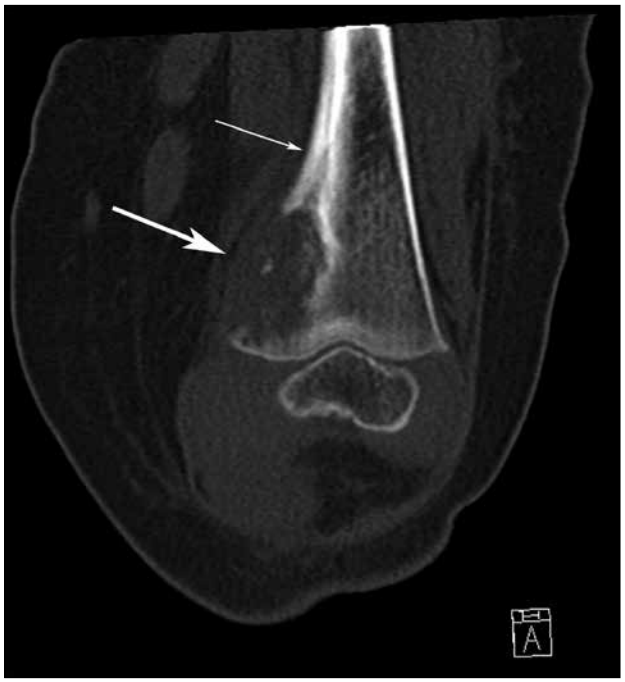

Figure 1. Coronal computed tomography image of distal left femur showing a destructive metaphyseal lesion with a permeative growth pattern, subperiosteal new bone formation (thin arrow) and a soft tissue mass (thick arrow).

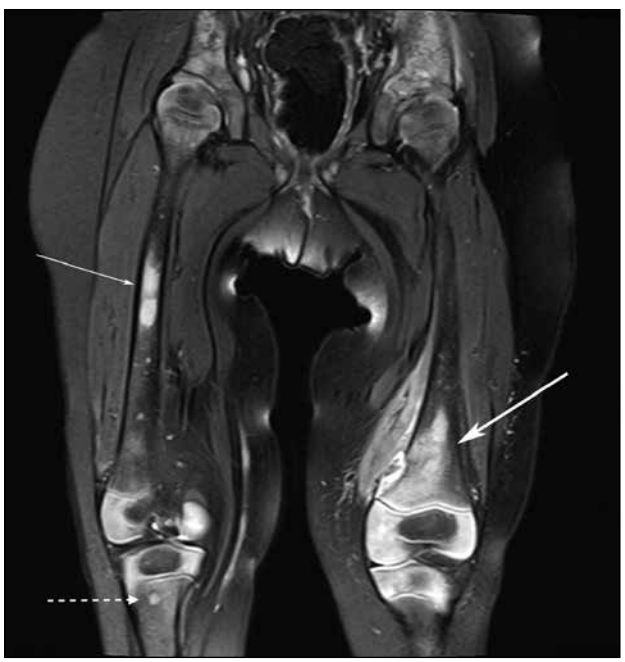

Figure 2. Fat-suppressed coronal T2-weighted magnetic resonance imaging of the thighs showing extensive signal abnormality in the distal left femoral metaphysis (thick arrow). There are asymptomatic lesions in the right femoral diaphysis (thin arrow) and right proximal tibial metaphysis (dashed arrow), and diffusely abnormal marrow signal in the pelvis.

During her diagnostic workup, she developed left-sided facial weakness with drooling. MRI demonstrated extensive calvarial marrow infiltration, with compression of the facial nerve by a left mastoid lesion, and extensive vertebral infiltration with pathological fractures. Cerebrospinal fluid examination was negative for malignant cells. Positron emission tomography–computed tomography (PET-CT) with ^{18}F-fluorodeoxyglucose revealed diffuse skeletal and splenic uptake. She was started on emergency chemotherapy with carboplatin and etoposide while awaiting confirmation of the final diagnosis.

The bone marrow aspirates and trephines revealed up to 20% blasts, with immunohistochemical staining showing the same characteristics as the bone biopsy. Cytogenetic assessment of the bone marrow aspirates revealed a 46,XX,der(7)t(7;16)(q36;p11.2),der(8)t(1;8)(q25;p23),der(16)inv(16)(p11.2q24)t(7;16)(q36;p11.2)[9]/46,XX[11] karyotype consistent with a neoplastic clone. Bone biopsies from her left iliac wing and tibia showed significant blast infiltration, strongly positive for CD33, CD34, CD117, CD16/56 and cytoplasmic CD3, but negative for cytoplasmic myeloperoxidase, HLA-DR, nuclear TDT, other B/T-cell markers (including CD7), and monocyte antigens.

Given these findings, a final diagnosis of ALAL was made, with features of AML and early T-cell precursor ALL. Given the predominance of myeloid markers, she was started on AML therapy according to the high-risk arm of the Children's Oncology Group AAML1031 study.

She demonstrated significant clinical improvement with this treatment, and bone marrow aspirates and trephines following the first cycle of definitive therapy revealed complete morphological and cytogenetic remission, with a very good partial response on PET-CT and brain MRI. At the end of treatment, following four cycles of therapy, she was in morphological, cytogenetic and radiological remission, but within a month of treatment completion she presented with pneumonia and left hip joint pain. MRI revealed multifocal areas of marrow infiltrate in the lumbar spine, pelvis, and proximal femora, with diffuse skeletal fluorodeoxyglucose avidity on PET-CT. An aspirate of a left hip joint effusion was consistent with disease relapse. An attempt was made to induce remission using T-cell ALL–based therapy, but she deteriorated rapidly and died of progressive disease.

DISCUSSION

The World Health Organization has recently updated its classification of ALAL after changes to its definition over the years.[1] ALAL is uncommon in children and is particularly rare in infancy. Its exact incidence is difficult to establish because of changes in definitions over the years, but accounts for approximately 3% of paediatric leukaemias.[2] There are no series specifically reporting the clinical features of ALAL, but it has been stated that fatigue, infections, and bleeding manifestations are common presentations.[2] Central nervous system involvement at the time of diagnosis has been reported in about 20% of children, significantly more often than in ALL.[3,4]

Children with ALL typically present with fever, bleeding, pallor, fatigue, rash, lymphadenopathy or organomegaly.[5] Bone involvement occurs at presentation in about one quarter of patients and radiological investigations usually reveal a diffuse pattern of bone change such as osteopenia or radiolucent metaphyseal bands, rather than one or more focal masses.[6] AML shares many of the clinical features of ALL. Other common manifestations of AML include gingival infiltration and leukaemia cutis.[5] Nonetheless bone involvement in paediatric AML is uncommon compared with ALL. Reports of focal bone lesions are sparse in ALL or AML, and this presentation has not been reported in children with ALAL. Ghodke et al[7] described an 8-year-old female who presented with swelling of her right cheek without other symptoms. Imaging revealed a solitary soft tissue mass in the right maxillary sinus and erosion of the alveolar process. Blood, bone marrow and cerebrospinal fluid examination were all normal. Immunophenotyping of a biopsy revealed both myeloid and lymphoid commitment, and a diagnosis of bi/mixed phenotypic blastic haematolymphoid neoplasm was made, as bone marrow was not involved.[7]

Our patient presented with pain, irritability and difficulty weight-bearing. CT showed a focal aggressive metaphyseal lesion. In contrast to most patients with ALL and AML, no systemic features were present at presentation and blood tests were essentially normal. Early diagnosis of ALAL can therefore be very challenging with this type of presentation. The differential diagnosis of a focal destructive bone lesion in younger children includes infection, Ewing sarcoma, metastasis (especially from neuroblastoma), and Langerhans cell histiocytosis, in addition to haematological malignancies. Because early diagnosis and treatment of acute leukaemia reduces morbidity and mortality,[8] a high degree of suspicion should be maintained in a child who presents with bone lesions.

In summary, ALAL is a rare form of acute leukaemia that can present with focal bone lesions in children. Our patient demonstrated the radiographic challenges in making an early diagnosis of acute leukaemia and serves as a reminder that this diagnosis should be considered in all children with destructive bone lesions.

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