CASE REPORT

Low-trauma Fracture with Hypercalcemia: Need to Look Deeper

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Abstract

Aim: To emphasize the importance of a timely, systemic approach to hypercalcemia to reach an etiological diagnosis.

Background: Hypercalcemia is commonly encountered in many individuals, in both inpatient and outpatient settings. Its evaluation entails careful history taking, a battery of investigations to arrive at an etiological diagnosis. Hypercalcemia is more common in adults but not uncommon in children and adolescents.

Case description: Here, we present a case of an apparently healthy young male presenting with a nontraumatic vertebral fracture who was incidentally detected to have hypercalcemia. Further evaluation revealed parathyroid hormone (PTH)-independent hypercalcemia. He also had mild anemia and mildly impaired renal function at presentation. During his in-hospital stay, he developed bicytopenia. Bone marrow studies and flow cytometry showed a hypercellular marrow suggestive of acute lymphoblastic leukemia (ALL).

Discussion: This case illustrates an uncommon presentation of aleukemic ALL, i.e., low-trauma fracture with PTH-independent hypercalcemia.

Conclusion: Hypercalcemia, especially PTH-independent, should entail a high index of suspicion across all age groups for malignancies, including solid tumors and hematological malignancies.

Clinical significance: Malignancies, even in younger individuals, can present with low-trauma fracture and hypercalcemia.

Keywords: Acute lymphoblastic leukemia, Hypercalcemia, Leukemia, Parathyroid-independent hypercalcemia, Pathological fracture.

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Background

Hypercalcemia is a common condition, estimated to occur in about 2% of the general population. It is largely attributed to primary hyperparathyroidism. However, hypercalcemia of malignancy is not uncommon, especially in adults. This entity is less commonly encountered in younger age groups. Here, we would like to report an unusual case of hypercalcemia in a young male.

Case Description

This 17-year-old male presented with complaints of lower limb pain, generalized weakness, and back pain for the last 4 months. The back pain was sudden in onset while he was trying to lift a pile of bricks. Subsequent evaluation revealed the collapse of multiple vertebrae. He had no history of abdominal pain, hematuria, graveluria, or abnormal behavior. There was no history of cough, fever, or exposure to any tuberculosis (TB) contact. He had no history of weight loss or decreased appetite. He had no history of addiction; his drug history was insignificant; and his past medical history was unremarkable. Family history was noncontributory, particularly in the context of bone disease.

In view of a possible low-trauma vertebral collapse, we decided to investigate him for metabolic bone disorders, including osteoporosis. The vertebral X-ray done 4 months back showed the collapse of multiple dorsal and lumbar vertebrae because of wedge fractures with rarefied bones (Fig. 1). Routine battery of tests done elsewhere revealed impaired renal function with an estimated glomerular filtration rate (GFR) of 54 mL/minute/1.73 m^2. Parathyroid hormone (PTH), vitamin D, and albumin levels were not determined at that time. There was, however, no evidence of lytic lesion or metastatic bone deposits.

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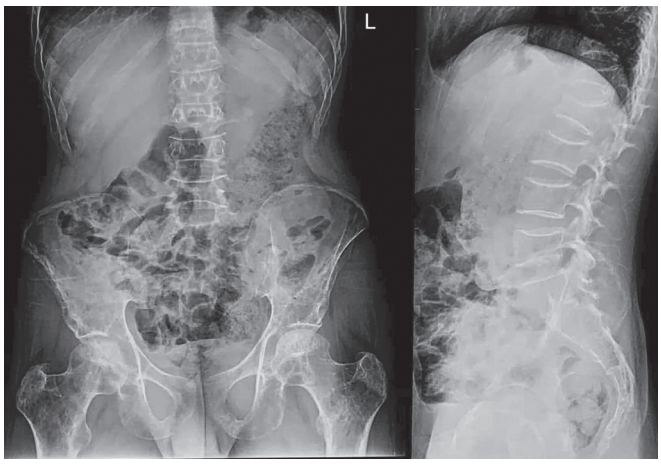


Fig. 1: Anteroposterior (AP) and lateral X-ray of spine shows rarefaction of bones with collapse of multiple dorsal and lumbar vertebrae

Upon presentation, he was conscious, oriented, and functional class 3 (wheelchair-bound, unable to walk). He had a lean body habitus with a body mass index (BMI) of 18.2 kg/m^2. He was normotensive and had mild pallor, tenderness over lower dorsal vertebrae, but no lymphadenopathy or any palpable neck mass. Systemic examination revealed no other abnormality.

Baseline investigations showed raised serum calcium with normal serum phosphorus, potassium, and magnesium levels (corrected serum calcium—12.94 mg/dL, phosphate—4.3 mg/dL, Sr K—4.0, Sr Mg—2.5 mg/dL). He had elevated alkaline phosphatase levels [alkaline phosphatase (ALP)—160 IU/L], and renal function [Sr Creatinine 1.76 mg/dL, estimated glomerular filtration rate (eGFR) by chronic kidney disease (CKD) epidemiology collaboration (EPI) 56 mL/minute/1.73 m^2] was mildly impaired. Serum 25-OH vitamin D levels (34 ng/mL) were normal, and PTH (6 pg/mL) was not raised. 1,25-OH vitamin D levels (<5 pg/mL) were low. Urinary calcium-creatinine ratio (547 mg/g creatinine) was suggestive of hypercalciuria. Hemogram upon admission revealed mild anemia [hemoglobin (Hb)—9.4 g/dL, mean corpuscular volume (MCV)—80 fL, thin layer chromatography (TLC)—6370/mm^3, N75 L21 M2 E2, platelet 1.96 lac/mm^3] with peripheral blood smears (PBS) pointing to a microcytic, hypochromic picture without any atypical cells. Serum protein electrophoresis did not reveal any M band. Ultrasound sonography (USG) of the abdomen was not suggestive of nephrolithiasis or nephrocalcinosis.

Treatment for hypercalcemia was initiated in the form of hydration and renal function adjusted dose of zoledronic acid. Repeat hemogram of the patient revealed bicytopenia (Hb—8.6 g/dL, TLC—3,800/mm^3, N77 L20 M1 E2, platelet—80,000/mm^3), and the PBS showed microcytic, hypochromic red blood cells (RBCs) with thrombocytopenia and no atypical cells. At this time, he had no lymphadenopathy, rash, petechiae, bleeding tendency, or hepatosplenomegaly.

As the patient had PTH- and vitamin-D-independent hypercalcemia with bicytopenia, a bone marrow study was planned. Bone marrow evaluation (Fig. 2) yielded a partially hemodiluted marrow aspirate which was hypercellular for age with a relative excess of atypical blastoid cells (14%) on examining the imprint smears. The blasts were 1.5–2 times the size of a mature lymphocyte with a high N:C ratio, irregular nuclear contour with focally indented nuclear membrane, slightly opened up chromatin, 1–2 inconspicuous nucleoli, and a scant amount of agranular basophilic cytoplasm. No Auer rods were seen. These blasts were negative for myeloperoxidase (MPO) on cytochemistry. Flow cytometry showed 10.4% blasts. Bone marrow biopsy showed hypercellular marrow spaces with interstitial excess of immature cells positive for terminal deoxynucleotidyl transferase (TdT) and CD20. A diagnosis of B-cell acute lymphoblastic leukemia (ALL) was confirmed. He was initiated on chemotherapy (daunorubicin, intrathecal methotrexate, vincristine, and prednisolone).

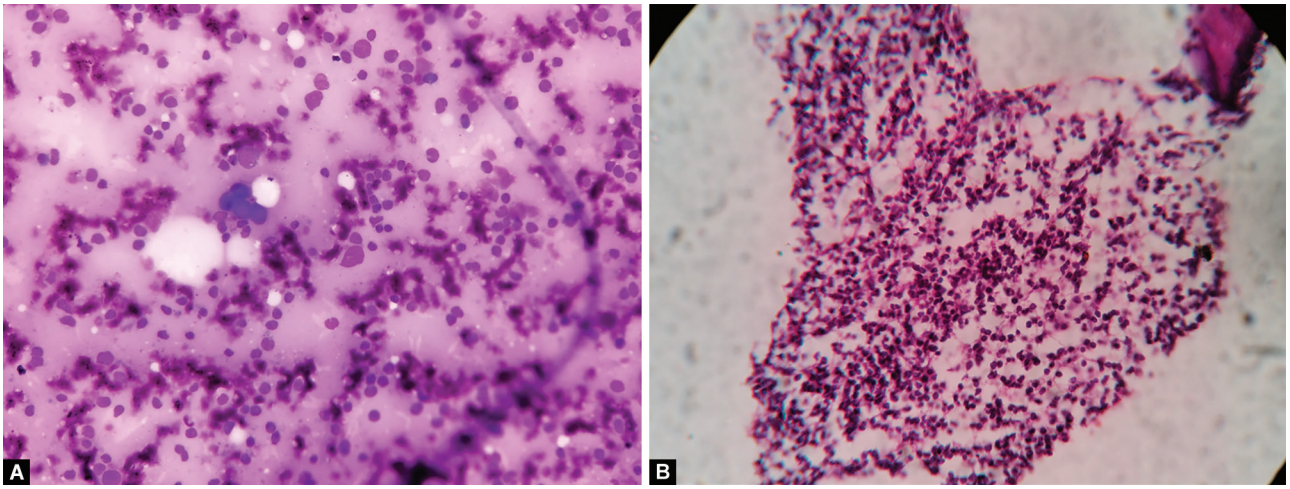
Unfortunately, he was lost to follow-up.

Discussion

This case highlights the rare presentation of leukemia in the form of PTH-independent hypercalcemia. Hypercalcemia is not uncommon in the general population, with a prevalence of 1–2%. Ninety percent of cases are due to primary hyperparathyroidism and malignancy.[1] Primary hyperparathyroidism is characterized by a long-standing, usually mild hypercalcemia. Hypercalcemia is a common finding in malignancy, especially lung carcinoma; it is often severe and difficult to manage.

Hypercalcemia of malignancy is common in adults, seen in up to 20% of cases. However, hypercalcemia is less frequently seen in children with an incidence of 0.4–1.3%.[2] Hypercalcemia of malignancy may be mediated by PTH-related protein (PTHrP) action (humoral hypercalcemia, seen in squamous cell carcinoma of the lung, renal tumors) or by local osteolytic activity (multiple myeloma, leukemia, and lymphoma). In hematological malignancies, local osteolytic activity is orchestrated by a cytokine (IL 1B,3, 6) and lymphotoxin [transforming growth factor beta (TGF-B)]-mediated receptor activator of nuclear factor kappa-B ligand (RANKL) overexpression. Some lymphomas can also lead to increased 1,25-OH vitamin D synthesis. Most malignancies produce hypercalcemia at an advanced stage. Hypercalcemia of malignancy often portends a poor prognosis with a life expectancy as low as 1–2 months after detection.[3]

Hypercalcemia is reported to occur more commonly in ALL as compared to acute myeloid leukemia (AML); incidence is reported to be 2.5–4.8%.[4,5] Children presenting with hypercalcemia tend to be older, "aleukemic" presentation (do not have markedly abnormal



Figs 2A and B: (A) Bone marrow aspiration smear shows admixture of peripheral blood elements and cluster of osteoblasts; (B) Bone marrow impression smear shows large blastoid cells with high nuclear/cytoplasmic ratio

hemograms and peripheral blood smears usually do not reveal any blasts)[5] as present in our case. Inukai et al. found an association between *t* (17,19) translocation resulting in E2A-hepatic leukemia factor (HLF) fusion transcription factor in subsets of ALL with hypercalcemia. This subset was also characterized by a less common immunophenotype (CD10-positive, CD19-negative).[6] However, this phenotype was not observed in the patient mentioned.

Clinical Significance

This case highlights the importance of stepwise analysis of hypercalcemia and timely evaluation of pathological fracture in all age groups, including children and adolescents. In the absence of classical features known to be associated with these malignancies, hypercalcemia may be the only diagnostic clue. Hypercalcemia, especially PTH independent, should entail a high index of suspicion across all age groups for malignancies, including solid tumors and hematological malignancies.

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