Chronic Myeloid Leukemia Associated Hypercalcemia: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Male, 58
Final Diagnosis: Hypercalcemia
Symptoms: Confusion • dehydration
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolism

Objective: Rare co-existence of disease or pathology
Background: Hypercalcemia associated with chronic myeloid leukemia (CML) is an ominous sign. Although rare, several cases have been reported and multiple pathophysiologic mechanisms have been independently proposed. We present a patient case and a literature review of the clinical presentation and mechanisms of CML-associated hypercalcemia.

Case Report: A 58-year-old male with a past medical history of CML diagnosed six years earlier, presented to the emergency department with one week of acute confusion, disorientation, polyuria, and polydipsia. On physical examination, we observed tachycardia, altered mental status, and dehydration. Blood analysis revealed leukocytosis, thrombocytosis, and marked hypercalcemia (18.6 mg/dL). His chest CT scan showed diffuse lytic lesions and bone destruction concerning for diffuse bone marrow involvement. The patient was diagnosed with hypercalcemia in the context of a CML blast phase. Treatment with hydration, calcitonin, and zoledronic acid lead to control of his symptoms and normalization of his serum calcium levels. After discharged, the patient was maintained on palliative treatment and zoledronic acid management without new episodes of hypercalcemia. However, eight months later, the patient died.

Conclusions: Evidence from the literature demonstrates a highly variable clinical presentation of CML-associated hypercalcemia, commonly occurring during an accelerated or a blast phase, and associated with poor survival. Multiple mechanisms could be involved and are not exclusive of each other. Better understanding of the pathophysiologic mechanisms involved in CML-associated hypercalcemia could lead to improvement in clinical and laboratory evaluation of these patients and be the foundation for the development of better management strategies and possibly target-directed therapy to positively improve prognosis.

MeSH Keywords: Case Reports • Hypercalcemia • Leukemia, Myelogenous, Chronic, BCR-ABL Positive

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Background

Hypercalcemia is a common electrolyte disturbance presenting as a metabolic emergency in up to 0.5% of hospitalized patients [1]. It is a well-known complication in cancer patients, with reports of hypercalcemia due to cancer reported as early as the 1920s [2]. Based on epidemiology and published reports, cancer-related hypercalcemia is most likely found in association with solid tumors, mainly in the lungs, breast, head/neck, and esophagus [3,4]. Only an estimated 15% of total cases correspond to hematological or immunological malignancies from which 50% are caused by lymphomas and the other 50% by myeloma and leukemia [1,3]. In retrospective studies, the incidence of hypercalcemia in all types of leukemia has been estimated to be 2.5% [5,6]. The occurrence of hypercalcemia in patients with chronic myeloid leukemia (CML) is very rare and limited cases have been reported [7].

CML-associated hypercalcemia may present as a severe life-threatening complication. In the clinical scenario of oncologic patients, it is important to consider this entity as a rare but possible etiology of hypercalcemia. We present a case of CML-associated hypercalcemia and a review of the current literature of previously reported cases of CML and hypercalcemia.

Case Report

A 58-year-old white American male presented to the emergency department (ED) with acute onset of confusion, disorientation, inability to walk steadily, and dehydration with associated generalized weakness, polyuria, and polydipsia over the previous week. He had been diagnosed with CML six years earlier, with no hematological response to multiple chemotherapy regimens; he was at that time on treatment with allopurinol and awaiting allogeneic bone marrow transplant. Vital signs on admission to the ED included heart rate of 104 bpm, blood pressure of 122/68 mm Hg and temperature of 99.7°F (37.6°C). There were no remarkable findings on physical examination except for altered mental status and dehydration. Laboratory evaluations were: hemoglobin 13.3 g/dL, white blood cell count 18.3×10⁷/L (neutrophils 79.6%, lymphocytes 7.2%, and monocytes 8.3%), and platelet count 910×10⁶/L. Serum levels were: calcium 18.6 mg/dL, phosphate 4.6 mg/dL, sodium 135 mEq/L, potassium 2.7 mg/dL, albumin 4.0 g/dL, creatinine 2.2 mg/dL, total bilirubin 0.9 mg/dL, alkaline phosphatase 125 IU/L, aspartate aminotransferase 41 IU/L, and alanine aminotransferase 71 IU/L. SPEP was negative for an M spike. Hormones and vitamins levels were: PTH 33.7 ng/mL, PTHrP 1.4 pg/mL (<2 pg/mL), 25-OH vitamin D 30.4 ng/mL (20–50 ng/mL) and 1,25 OH vitamin D 30.4 ng/mL (20–50 ng/mL) and 1,25 OH vitamin D 30.4 ng/mL (20–50 ng/mL). Chest CT scan showed diffuse lytic lesions and bone destruction throughout the visualized thoracic skeleton, concerning for diffuse bone marrow involvement.

The clinical history and biochemical findings led to a diagnosis of CML-associated hypercalcemia in the context of a blast phase. Treatment with aggressive hydration with 0.9% saline and calcitonin 400 units subcutaneous was administered. Additionally, zoledronic acid 3.3 mg intravenous, adjusted for renal insufficiency, was given. After five days of treatment, normalization of symptoms and serum calcium levels were achieved. After discharge from the hospital, the patient continued with palliative treatment with ponatinib and radiotherapy. Acceptable serum calcium levels were maintained with zoledronic acid 4 mg every eight weeks. Despite these therapies, his cancer progressed and he passed away approximately eight months after the initial admission for hypercalcemia.

Discussion

Our extensive literature search found over 30 reported cases, most of which were last reviewed in 2007 [8]. Among the published results, the median participant age at presentation was 44 years. Most cases were terminal events and occurred during a blast crisis, both myeloid and lymphoblastic, or accelerated phase of CML. The median survival rate was two months [9–11]. It is impossible to describe a standardized clinical and pathophysiological presentation based on previously reported cases because most of them were highly variable and not all the patients underwent complete workup to definitely include or exclude all the possible causes described in this report.

PTHRP is a protein that exerts certain PTH like effects [2]. It can be produced and released not only from tumor cells but from normal tissue and act on PTH receptors [2,6,9]. This polypeptide, in a similar fashion to PTH, is implicated in hypercalcemia by stimulating bone resorption and increasing renal calcium reabsorption, and releasing calcium into serum [8,9,12,13]. Although not commonly elevated in hematological malignancies [9], previous studies have demonstrated elevated mRNA for PTHrP in cultured leukemic cells, as well as increased plasma levels in patients with T-cell leukemia and B-cell lymphoma [7,8,14].

In several cases, PTHrP has been reported to be elevated as an isolated etiologic agent or together with other possible causes of CML-associated hypercalcemia [7,8,14,15]. Unfortunately, measurements of PTHrP levels have only been reported in recent case reports [16]. Additionally, there have been reports in which serum PTHrP levels were normal but PTHrP involvement in the pathogenesis of hypercalcemia was not fully excluded since it was rapidly degraded extracellularly, and thus it was proposed that PTHrP could also act in a paracrine way inducing direct osteoclastic activity on bone [9,12,13].

Considering that elevated PTH, mainly due to alterations in parathyroid glands secretion, is one of the main etiologies of
all cause hypercalcemia [17], it is measured as part of the ini-
tial assessment of patients with CML-associated hypercal-
cemia in an attempt to identify any possible role as a causative 
factor. Elevation in the level of PTH is rare but reported in up 
to 18% of patients with calcium disturbances associated with 
haematological malignancies [9,12]. Previous reports identi-
ﬁed two CML-associated hypercalcemia cases in which PTH 
was elevated due to concomitant primary hyperparathyroid-
ism [6,18], and there is one report of elevated PTH levels due 
to ectopic production by leukemic blasts [19].

Some grade of osteolysis was present in the majority of the 
reported cases without a clear attributable pathogenesis de-
scribed [8]. From initial reports, there are several cases of pa-
tients in which osteolytic lesions were the only factor involved 
in the pathogenesis of CML-associated hypercalcemia as well 
as multiple other cases in which other possible mechanisms 
were found concomitantly [1,5,13,20,21]. Hypercalcemia in pa-
tients with CML may result from localized bone destruction 
due to a direct effect of tumor cells [5].

Direct bone injury is mostly reported in breast cancer, multiple 
myeloma, and hematological malignancies, and consists of bone 
resorption due to the direct effect of metastatic tumor cells or 
monocytes that are in contact with bone [2,3]. Speciﬁcally in 
CML, it has been reported that a localized blast crisis could 
compromise bone and generate direct tissue destruction, which 
could explain elevated serum calcium levels [5,20].

However, there are reports of patients with hypercalcemia 
without skeletal lesions in which the absence of radiograph-
ic abnormalities does not exclude the action of osteolytic fac-
tors contributing to hypercalcemia [10]. Evidence supports 
the role of other causative humoral factors besides direct bone in-
volve ment in the pathogenesis of CML-associated hypercalce-
 mia [2,6,13]. Unfortunately, there have been only a few cases in 
which humoral mediators have been measured and ﬁnd-
ings have been variable, ranging from normal levels to eleva-
tion of one or several mediators [7].

Humoral mediated osteolysis has been demonstrated by os-
teoclastic bone resorption triggered by circulating factors that 
have been secreted remotely from bone by malignant cells [2]. 
Most of these factors have been found to cause osteolysis in 
vitro but have not been established as playing a predominant 
role as solitary triggers in the pathogenesis of hypercalcemia 
in vivo in hematological malignancies. However, when adding 
the effect of the multiple related factors that act concomitant, 
it has been hypothesized that their osteolytic potency is aug-
mented [12,22,23].

It is widely known that myeloma and lymphoma produce osteo-
clast activating factors such as interleukin 1 (IL-1α), interleukin 
6 (IL-6), tumor necrosis factor alfa (TNF-α), tumor necrosis fac-
tor beta (TNF-β), tumor growth factor beta (TGF-β), and mac-
rophage inﬂammatory protein (MIP 1-α). These factors are 
normally produced in small amounts by normal lymphocytes 
and, although rare, may also be produced in malignant cells 
in patients with CML [9,12]. The role of IL-6 has speciﬁcally 
been studied. A clear relation between the levels of IL-6 and 
cell growth in myeloma has been established; however, there 
is no relation with hypercalcemia itself. Moreover, augmented 
IL-6 levels in other inﬂammatory processes have no correlation 
with hypercalcemia or higher bone resorption [9]. Deﬁnitive 
data on the role of IL-6 and other mentioned factors on CML-
associated hypercalcemia is lacking.

Furthermore, prostaglandins E (PGE) and prostaglandin F (PGF), 
which have demonstrated osteolytic activity in bone culture as-
says, can have signiﬁcantly higher expression by tumor, bone, 
and immune cells compared to normal tissue as corroborat-
ed by animal studies and breast cancer case reports [3,8,15]. 
Although lymphocytes can secrete elevated amounts of osteo-
clast activating factor in hematological malignancies, the levels 
do not correlate with the development of hypercalcemia [24]. 
Moreover, monocytes and macrophages secrete osteolytic pros-
taglandins but have been found to have normal prostaglandin 
E2 (PGE2) production when compared with normal patient; 
however, studies suggest that these cells might secrete an-
other yet undescribed potent osteolytic factor different from 
PGE [3,25]. Additionally tumor growth factor alfa (TGF-α) and 
TGF-β, which induce RANK ligand expression in vascular cells 
derived from bone, were reported elevated along with PGE2 in 
the serum of a patient with CML-associated hypercalcemia [8].

Osteolysis is not a completely well-characterized process, and 
there is no known relation between the severity of hypercal-
cemia and the presence or absence of osteolytic lesions [13]. 
It is therefore important to consider that direct injury and hu-
oral mechanisms are not mutually exclusive; in fact these 
events might act concomitantly to trigger bone resorption in 
CML patients presenting with hypercalcemia [13,15].

Several additional mechanisms have been proposed; but these 
lack strong evidence to support their possible role in the patho-
genesis of hypercalcemia in CML patients. Trying to extrapolate 
information from other malignancies, the possible role of vita-
im D has also been studied. In vitro upregulation of renal hy-
droxylilation of 1,25 OH vitamin D by PGE2 stimulation has been 
reported [26]. However, despite upregulation of this metabo-
lite, it appears that vitamin D is not involved in the pathogen-
esis of hypercalcemia in CML since improvement on calcium 
levels has not been seen with corticosteroid administration [6].

Our patient presented with severe hypercalcemia directly at-
tributable to CML with age of presentation and phase of the
disease compatible with previously reported epidemiology. His PTH level was low and his 1,25 OH vitamin D$_3$ level was normal, so concomitant primary hyperparathyroidism and vitamin D overproduction were excluded. His PTHrP level was also undetectable. Osteolytic lesions were the main contributory factor in the pathogenesis of hypercalcemia in this case, confirmed by radiologic findings. Unfortunately, humoral markers were not measured, so their role could not be assessed.

Conclusions

Hypercalcemia is one of the most common paraneoplastic syndromes and, although rare, it has been reported in CML patients [1,8]. Clinical presentation is highly variable but usually presents during a blast or accelerated crisis and constitutes an ominous sign with a devastating prognosis [10,11]. Multiple possible mechanisms have been described, and it has been found that one or multiple etiologic factors could be involved at the same time and are not exclusive of each other.

PTH levels are low in most cases but have been reported to be elevated in the context of concomitant parathyroid adenoma, and there was one report of ectopic production in cancer cells [18,19]. PTHrP levels can be normal or elevated [7,15]. On the other hand, skeletal tumor compromise is one of the main causes of hypercalcemia in CML and both local bone involvement and humoral factors have been proposed. Additionally, multiple humoral factors have been evaluated in vitro and have been found to be produced by malignant cells, but their osteolytic role and potency as isolated factors in vivo is not clear [9,12,22]. Among the studied factors only TGF-α, TGF-β, and PGE2 have been reported elevated in a CML patient with a clear attributable role in the pathogenesis [8].

Unfortunately, not all the reported cases, like ours, have had extensive workup for all the proposed possible mechanisms, and additional data are needed to determine other possible mechanisms involved. This review hopes to set the foundation for further clinical and laboratory evaluations of patients with CML-associated hypercalcemia so that better characterization and understanding of the pathogenesis can lead to more appropriate and possibly target-directed therapy to finally improve prognosis for these patients.

Competing interests

The authors declare they have no competing financial interests.
24. Humes JL, Bonney RJ, Pelus L, et al: Macrophages synthesise and release prostaglandins in response to inflammatory stimuli. Nature, 1977; 269(5624): 149–51
25. Kurland JI, Bockman R: Prostaglandin E production by human blood monocytes and mouse peritoneal macrophages. J Exp Med, 1978; 147(3): 952–57
26. Wark JD, Taft JL, Michelangeli VP, et al: Biphasic action of prostaglandin E2 on conversion of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 in chick renal tubules. Prostaglandins, 1984; 27(3): 453–63