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

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

Objective: Rare co-existance 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

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/902467

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 allogenic 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 18.3×10^9/L (neutrophils 79.6%, lymphocytes 7.2%, and monocytes 8.3%), and platelet count 910×10^9/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 8.5 pg/L (15–65 pg/L), PHTrP 1.4 pg/L (<2 pg/L), 25-OH vitamin D 30.4 ng/mL (20–50 ng/mL) and 1,25 OH vitamin D_3 33.7 ng/mL (18–64) 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 pathophysiologic 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 initial assessment of patients with CML-associated hypercalcemia 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 hematological malignancies [9,12]. Previous reports identified two CML-associated hypercalcemia cases in which PTH was elevated due to concomitant primary hyperparathyroidism [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 described [8]. From initial reports, there are several cases of patients 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 patients 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 radiographic abnormalities does not exclude the action of osteolytic factors contributing to hypercalcemia [10]. Evidence supports the role of other causative humoral factors besides direct bone involvement in the pathogenesis of CML-associated hypercalcemia [2,6,13]. Unfortunately, there have been only a few cases in which humoral mediators have been measured and findings have been variable, ranging from normal levels to elevation of one or several mediators [7].

Humoral mediated osteolysis has been demonstrated by osteoclastic 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 augmented [12,22,23].

It is widely known that myeloma and lymphoma produce osteoclast activating factors such as interleukin 1 (IL-1α), interleukin 6 (IL-6), tumor necrosis factor alfa (TNF-α), tumor necrosis factor beta (TNF-β), tumor growth factor beta (TGF-β), and macrophage 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 assays, can have significantly higher expression by tumor, bone, and immune cells compared to normal tissue as corroborated by animal studies and breast cancer case reports [3,8,15]. Although lymphocytes can secrete elevated amounts of osteoclast activating factor in hematological malignancies, the levels do not correlate with the development of hypercalcemia [24]. Moreover, monocytes and macrophages secrete osteolytic prostaglandins but have been found to have normal prostaglandin E2 (PGE2) production when compared with normal patient; however, studies suggest that these cells might secrete another 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 hypercalcemia and the presence or absence or osteolytic lesions [13]. It is therefore important to consider that direct injury and humoral 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 pathogenesis of hypercalcemia in CML patients. Trying to extrapolate information from other malignancies, the possible role of vitamin D has also been studied. *In vitro* upregulation of renal hydroxylation of 1,25 OH vitamin D by PGE2 stimulation has been reported [26]. However, despite upregulation of this metabolite, it appears that vitamin D is not involved in the pathogenesis of hypercalcemia in CML since improvement on calcium levels has not been seen with corticosteroid administration [6].

Our patient presented with severe hypercalcemia directly attributable 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.

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