

# Symptomatic Hypercalcemia in a Patient with B-cell Chronic Lymphocytic Leukemia – A Case Report and Review of the Literature

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**Abstract.** *Background: Hypercalcemia due to malignancy is well described in the literature and a common paraneoplastic finding in certain solid tumors. Hematologic malignancies, however, are less frequently associated with hypercalcemia with the exception of myelomas and T-cell lymphomas. Case report: This case report describes a patient with B-cell chronic lymphocytic leukemia (B-CLL) who developed symptomatic hypercalcemia. None of the pathogenetic mechanisms of malignancy-associated hypercalcemia already described in the literature could explain the pathogenesis of hypercalcemia in our patient. Calcium levels were normalized after initial treatment and remained within normal limits following treatment of the underlying B-CLL. The follow-up period was 26 months. The normalization of calcium levels was closely associated with the drop in the absolute lymphocyte count. Conclusion: Symptomatic hypercalcemia in B-CLL is exceedingly rare and only documented a few times in the literature. Hypercalcemia, in the present case, was not caused by any of the mechanisms already described in the literature and responded well to treatment of the underlying B-CLL.*

Hypercalcemia of malignancy is a common disorder in patients with solid tumors but not as common in hematologic malignancies (1). Some lymphoplasmatocytic dyscrasias, including adult T-cell lymphoma/leukemia and multiple myeloma, are known to be accompanied by hypercalcemia (2). However, B-cell chronic lymphocytic leukemia (B-CLL)

and hypercalcemia are rarely seen together and only a few cases have been reported in the literature.

Malignancy-associated hypercalcemia may be divided into three major categories based on the pathogenetic mechanism (Figure 1): (i) local osteolytic hypercalcemia by activation of osteoclasts by either a primary bony tumor or metastases (a variety of cytokines, including tumor necrosis factor-beta (TNF-beta), interleukin (IL)-1beta, IL-6, have been implicated), (ii) humoral hypercalcemia, which is mediated by the production of systemic hormonal factors, usually the parathyroid hormone-related peptide (PTHrP) and is the most common cause in patients with solid tumors and (iii) 1,25 dihydroxy vitamin D (calcitriol) mediated hypercalcemia, which is induced by dysregulated production of calcitriol by the tumor cells and is the most common mechanism in Hodgkin's and non-Hodgkin's lymphoma (2, 3). In chronic lymphocytic leukemia (CLL) patients specifically, presence of hypercalcemia is very rare and has been attributed to similar mechanisms. In this report, we present a case of a patient with B-CLL who presented to the hospital with symptomatic hypercalcemia; no pathogenetic mechanism was identified despite a thorough workup.

## Case Report

A 70-year-old white male with past medical history significant only for hypertension controlled with lisinopril was referred to our clinic for evaluation of lymphocytosis in December of 2009. The patient had no active symptoms and physical exam was non significant on presentation. On further work up, flow cytometry of peripheral blood revealed CD5(+), CD23(+), CD43(+), surface kappa restricted B cell population consistent with B-CLL/small lymphocytic lymphoma (SLL). The patient had one favorable prognostic marker (Zap-70 was negative) and two unfavorable (positive CD38 and del11q). Since he had early stage disease at

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diagnosis (stage 0), no treatment was initially given and he was followed closely (every 3 months) with laboratory analysis. In July of 2011, the patient presented with generalized lymphadenopathy of the neck, axilla and inguinal regions, effectively advancing his stage to 1. He continued to have a normal hemogram and was otherwise asymptomatic until October of 2013 when he presented with fatigue, polyuria and constipation and found to have worsening anemia, worsening lymphadenopathy, hypercalcemia and renal insufficiency.

The patient was admitted and given aggressive hydration with normal saline. His admission labs were white blood count  $109 \times 10^3/\text{mm}^3$  (lymphocytes 93.6%, neutrophils 4.5%, monocytes 1.5%, eosinophils 0.0%, basophils 0.3%), hemoglobin 9.1 g/dl, platelets  $189 \times 10^3/\text{mm}^3$ , creatinine 3.0 mg/dl and calcium of 13.1mg/dl (reference range=8.4-9.8) with albumin of 4 mg/dl. The next day he was started on *i.v.* bisphosphonates (pamidronate). His calcium level increased to 13.9 mg/dl before returning within normal limits with treatment. His renal function returned to baseline as well. Parathyroid hormone (PTH) was appropriately suppressed to 5.9 pg/ml (14-72). PTHrP was  $<0.74$  pmol/l with normal values being  $<2$  pmol/l and thyroid-stimulating hormone (TSH) was 1.27 IU/ml (0.4-4 IU/ml). 1,25 Dihydroxy vitamin D levels (calcitriol) were 44.2 ng/dl (30-100 ng/dl). Beta 2 microglobulin was 13.1 mg/l (0.6-2.4 mg/l). Lactate dehydrogenase, haptoglobin, ferritin, vitamin B12, folate and immunoglobulins were all normal. Protein electrophoresis was normal as well. A computerized tomography (CT) of the chest, abdomen and pelvis was performed and showed extensive lymphadenopathy throughout the chest, abdomen and pelvis and marked splenomegaly. Bone scan was negative. A repeat flow cytometry was again consistent with B-CLL/SLL. No large cell or prolymphocytic transformation was evident and Richter's syndrome was excluded. Bone marrow aspirate and biopsy revealed an overall cellularity of approximately 50-60% (hypercellular) with the normal marrow elements being largely replaced by small mature lymphocytes (90% of cells) consistent with marrow involvement by CLL (Figures 2 and 3). Biopsy findings of two cervical lymph nodes were morphologically and immunophenotypically consistent with nodal involvement by B-CLL/SLL. The patient was treated as Rai stage 3 with bendamustine and rituximab. He overall received 6 cycles of the bendamustine-rituximab followed by maintenance rituximab every 3 months with excellent clinical and biochemical response. He tolerated treatment well except for myelosuppression, which required filgrastim support and dose reduction after cycle 2. Calcium levels normalized after initial treatment and remained within normal limits following treatment of the underlying B-CLL. The follow-up period was 26 months. The normalization of calcium levels was closely associated with the drop in the absolute lymphocyte count (Figure 4).

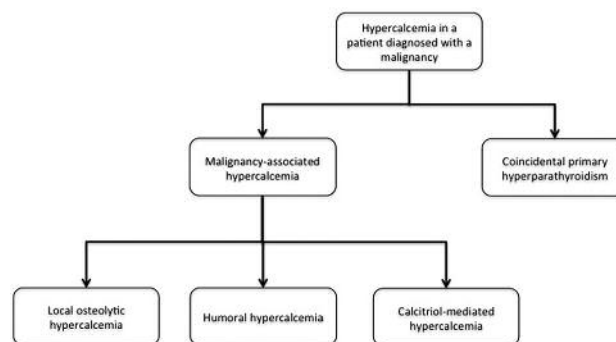


Figure 1. Reported pathogenetic mechanisms of hypercalcemia in malignancy.

## Discussion

Hypercalcemia is a well-described, metabolic disturbance involved in a multitude of malignancies (1). It is most commonly associated with solid tumors, such as breast cancer, non-small cell lung cancer and advanced-stage squamous cell tumors of the head and neck where it is usually attributed to the production of humoral factors, including PTHrP (4). Hypercalcemia is a rare occurrence in hematological malignancies with the exceptions of myelomas and T-cell lymphoma (5, 6). In B-cell lymphomas, hypercalcemia has been described less frequently and usually only in the setting of high-grade lymphomas (2).

Hypercalcemia in B-CLL is extremely rare with less than 30 cases reported in the English literature of the last 50 years (3, 7-9). In a retrospective study of 1,200 patients with B-CLL, only 7 patients (0.006%) were found to have high calcium levels (10)

Several pathogenetic mechanisms of hypercalcemia in B-CLL patients have been described. One of them includes the production of PTHrP, which has similar actions to PTH, and leads to increased skeletal and renal absorption of calcium (4, 7-9). In 1994, Fain *et al.* suggested that PTHrP plays a role based on the detection of *PTHrP* mRNA from *post-mortem* samples of liver, spleen and lymph node tissue infiltrated with leukemic cells, although serum PTHrP levels were not measured (10). In addition, dysregulated production of calcitriol (1,25-dihydroxyvitamin D) has been shown to be the etiology of hypercalcemia in some B-CLL patients (10). It is postulated that the mechanism is similar to that of hypercalcemia due to sarcoidosis; however, it is unknown whether the primary source of calcitriol are leukemia cells or surrounding macrophages (2). In other reports, hypercalcemia has been observed in patients with transformation of CLL to prolymphocytic leukemia or large cell (immunoblastic) lymphoma (Richter's syndrome) (11, 12). Richter's syndrome is defined as a high-grade

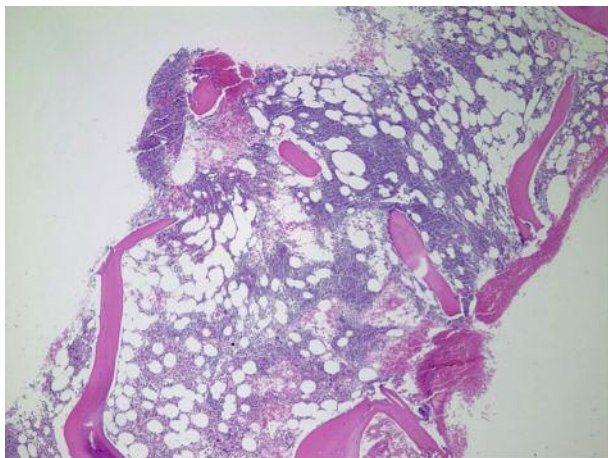


Figure 2. Bone marrow involved by chronic lymphocytic leukemia – 5× magnification image showing replacement of normal marrow elements by disease.

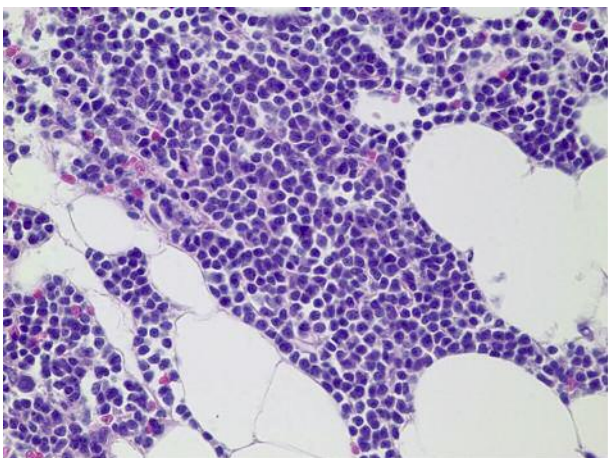


Figure 3. Neoplastic lymphoid infiltrate as seen in 40× amplification. High-power view of chronic lymphocytic leukemia – neoplastic small lymphoid cells effacing marrow elements.

lymphoma that develops during the progression of a low-grade lymphoproliferative disease (11). The presumed pathogenesis of hypercalcemia is the release of serum cytokines TNF- $\alpha$  and IL-6, which are thought to increase bone resorption. The frequency of large B-cell transformation is 3-6% and tends to have poor prognosis with a survival time averaging less than 5 months (12). Hypercalcemia in B-CLL patients has also been attributed to coincidental presence of primary hyperparathyroidism (13, 14). Finally, it has been suggested, by a single report, that hypercalcemia can be caused by classical CLL without any of the above mechanisms being involved (15). In our case,

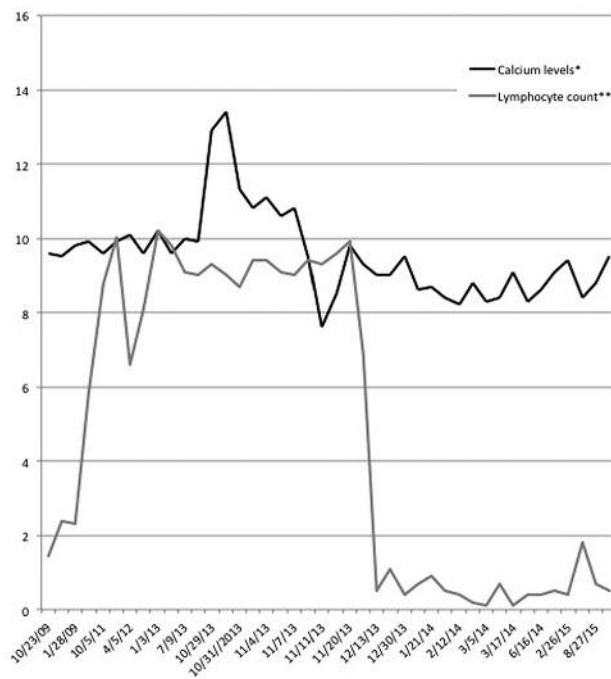


Figure 4. Association of calcium levels with absolute lymphocyte count levels in B-cell chronic lymphocytic leukemia patient throughout the follow-up period. \*Calcium levels measured in mg/dl and corrected for albumin. \*\*Absolute lymphocyte count levels measured in 10<sup>4</sup>/mm<sup>3</sup>.

the low serum PTH, low PTHrP, normal calcitriol levels, absence of any obvious solid tumor, multiple myeloma or signs of Richter's transformation and response to chemotherapy support that last scenario.

In the acute setting, treatment of hypercalcemia in CLL consists of parenteral hydration with normal saline and agents to suppress bone resorption, including calcitonin and bisphosphonates. Maintenance therapy is usually achieved through the use of bisphosphonates and treatment of the underlying disease (7). In the present case, patient's calcium levels returned to normal with hydration and bisphosphonates and remained within normal limits with the administration of chemotherapy and suppression of the leukemic cells (Figure 4).

Hypercalcemia of malignancy is considered to be a negative prognostic factor in a number of hematological malignancies. Direct therapies to prevent this complication have been shown to improve outcomes. In the setting of CLL, it is unknown if hypercalcemia is indicative of poor outcomes. However, it is suggested that, although presence of coincidental primary hyperparathyroidism as a cause of hypercalcemia, does not significantly affect patients' survival; patients with hypercalcemia without elevated PTH seem to have a terminal stage of the disease (13).

In conclusion, the present report describes a very rare case of a patient with B-CLL who presented with symptomatic hypercalcemia of cryptogenic pathogenesis and responded well to acute and maintenance treatment. Future research on the pathogenesis of hypercalcemia in CLL will increase our understanding on the disease and potentially help with appropriate management of these patients.

### Conflicts of Interest

None of the Authors have any potential conflicts (financial, professional or personal) that are relevant to the manuscript.

### Funding

Own resources.

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