Case Report

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# An Uncommon Presentation of Hypercalcemia in Chronic Lymphocytic Leukemia

Anan Promrattanakun, M.D.[1], Pongrat Niramitmahapanya, M.D.[1]

[1]Department of Medicine, Saraburi Hospital, Saraburi, 18000, Thailand

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**Abstract:**

Hypercalcemia is a common paraneoplastic syndrome in both solid and hematologic malignancies. There are three mechanisms involving in hypercalcemia. Firstly, the cancer increases the resorption of bone minerals resulting in releasing calcium and phosphate into plasma. Secondly, parathyroid hormone-related peptide (PTHrP) increases a reabsorption of calcium and excretion of phosphate at kidneys. Finally, calcitriol (1,25 dihydroxy vitamin D) induces vitamin D absorption in small bowel. Multiple myeloma or T-cell leukemia-lymphoma are usually presented with a symptomatic hypercalcemia. However, chronic lymphocytic leukemia (CLL) is uncommonly associated with hypercalcemia. Hypercalcemia occurring in CLL patients mostly indicates a relapsed or a refractory disease. In addition, it may imply an advanced stage as well as the transformation of disease to Richter's syndrome. This report presents an 81-year-old woman diagnosed with CLL, Rai stage III. She developed symptomatic hypercalcemia with an osteolytic lesion at left iliac wing together with an increased absolute lymphocyte count.

**Keywords:** Chronic lymphocytic leukemia, Hypercalcemia, Paraneoplastic syndrome, Osteolytic lesion

## Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the western world and it frequently affects the elderly at a median age of 72 years.[1] The incidence of CLL is not known in the USA but accounting for 1.2% of all new cancer cases.[2] In Thailand, the incidence of CLL is around 1.5% of new cancer cases between 2007 and 2014. The median age of CLL patients in Thailand was around 60 years old.[3] CLL is a chronic disease and not all cases need chemotherapy. A combination of chemotherapy was administered in patients with an advanced stage, symptomatic, organomegaly, lymphadenopathy and progressive lymphocytosis in order to improve quality of life and prolong survival.[4, 5] Previously, a complete remission rate has been reported around 41% of managed cases and the 5-year overall survival was 52%.[3]

Prevalence of hypercalcemia in all malignancies is 0.67% and the most common cancers associating with this condition are lung cancers, multiple myeloma, and renal cell carcinoma.[6] Hypercalcemia in CLL is uncommon and was rarely reported. Usually, organomegaly, lymphadenopathy, anemia and constitutional symptoms are common clinical findings at presentation in Thai CLL patients.[7] CLL patients presenting with hypercalcemia has been reported in few literatures and was only 7 patients in 1,200 (0.58%).[8]

Corresponding author: Anan Promrattanakun, M.D.
Department of Medicine, Saraburi Hospital, Saraburi 18000, Thailand
E-mail: thecoolsummer@hotmail.com

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The purpose of this report is to present a condition of symptomatic hypercalcemia in an 81-year-old woman who was diagnosed with advanced stage CLL.

**Case Presentation**

An 81-year-old woman with medical history of hypertension, dyslipidemia and chronic kidney disease stage 3B. Her metabolic diseases were controlled with amlodipine, losartan and simvastatin. She was transferred to Saraburi hospital for an evaluation of slipping and falling. The x-ray of lumbosacral spine revealed no fracture but her complete blood count showed lymphocytosis. She noticed constipation and malaise for one week. She did not have any fever, night sweating, weight loss or backache.

The physical examination revealed anemia together with enlargement of multiple lymph nodes along both anterior cervical regions. Other body parts were unremarkable. The initial blood tests were WBC 204.7 x $10^9$/L, PMN 15%, L 83%, M 1%, atypical L 1%, platelets 226.0 x $10^9$/L, hemoglobin 8.6 g/dL, hematocrit 27.5%, MCV 94.5 fL, MCH 29.6 pg, MCHC 31.3 g/dL, and RDW 14.6%. The blood chemistry profiles showed BUN 38.7 mg/dL, creatinine 1.82 mg/dL, eGFR 25.67 mL/min/1.73 $m^2$, corrected calcium 14.8 mg/dL, phosphate 4.2 mg/dL, and iPTH 5.12 pg/mL (15-88). Otherwise, normal liver function tests and serum electrolytes. Electrocardiogram showed normal QTc interval. Her blood smear showed numerous small-matured lymphocytes with non-cleaved nuclei and smudge cells (Figure 1).

Markers of peripheral blood flow cytometry were positive for CD19, CD5, CD23, but negative for FMC-7 and dim CD20. These markers were typically presented in CLL. Her bone marrow smear supported the diagnosis of CLL which showed hypercellularity, 85% infiltrated by small matured lymphocytes with non-cleaved nuclei, markedly decreased myeloid and erythroid series, and no abnormal large-sized mononuclear cell (Figure 2). The majority of cells in the bone marrow biopsy were small mature lymphocytes with partially positive for CD20 and Bcl-2, strongly positive for CD5, focal positive for CD23, and negative for cyclin D1 and MPO (Figure 3). These results suggested that she had CLL infiltrating in the bone marrow, and therefore stage III (Binet C) CLL was diagnosed in this patient.

Because hypercalcemia presented in this patient and we were aware of a severe form called Richter's syndrome. Therefore, lymph node biopsy was done to identify this syndrome. Pathological profiles of cervical lymph nodes revealed diffuse infiltration by small lymphoid cell with proliferation center. No morphologic evidence of large cell transformation or plasmacytic differentiation were noted. The neoplastic cells marked focally positive for CD5, CD43, faintly positive for CD23, CD20, CD3, CD10, and negative for cyclin D1. There were occasional CD20 staining at medium to large-sized B-cells which also showed low Ki-67 (<10%) (Figure 4). CT chest and whole abdomen showed multiple para-aortic and mesenteric lymph nodes at size up to 1.8x1.5 cm. An ill-defined osteolytic lesion was detected at left iliac wing. Otherwise, liver and spleen are unremarkable (Figure 5). We concluded that she did not develop Richter's syndrome.

The final diagnosis was CLL Rai staging system III (Binet C) presenting with symptomatic hypercalcemia with osteolytic bone lesion.

**Management**

An aggressive normal saline resuscitation was given for treating hypercalcemia in this case. Intravenous zoledronic acid was contraindicated in this patient due to acute kidney injury with decreased creatinine clearance to 19 mL/min. The serum calcium level turned to normal range within 6 days. While she was waiting for flow cytometry reports, her renal function returned to baseline.

Consequently, chlorambucil and prednisolone were prescribed regarding to poor performance status (ECOG 3), aging, and limited financial condition. She was currently receiving second cycle of a monthly 5-day course of chlorambucil/prednisolone without serious adverse side effect.

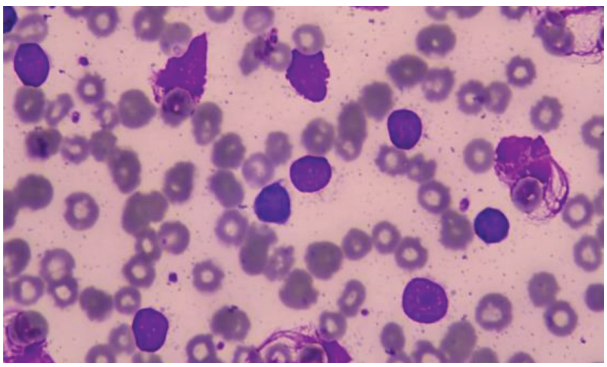

**Figure 1** Blood smear showed numerous non-cleaved nucleus of small-matured lymphocyte. (x100)

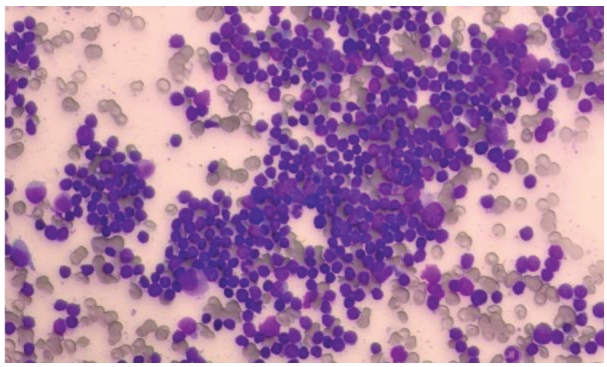

**Figure 2** Bone marrow smear showed small matured lymphocytes with non-cleaved nuclei, markedly decreased myeloid and erythroid series, and no abnormal large-sized mononuclear cells. (x100)

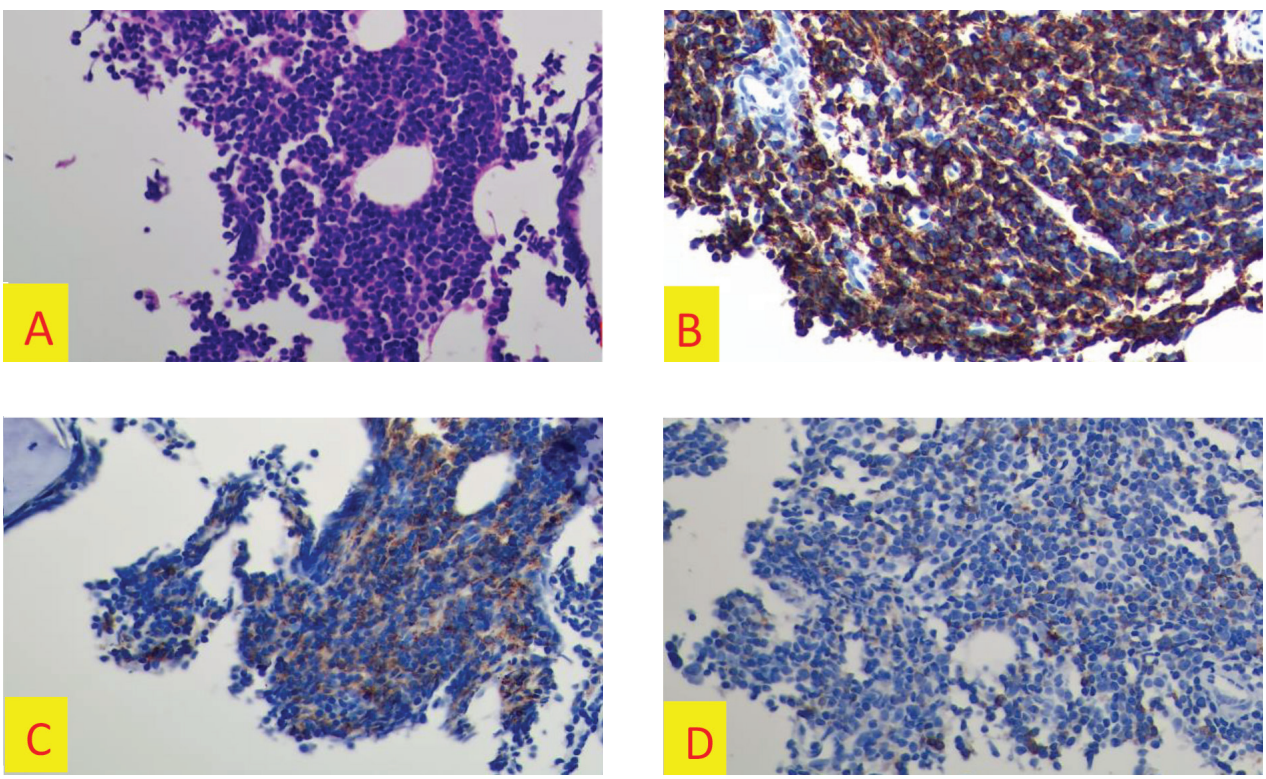


**Figure 3** Bone marrow core biopsy
A: H&E staining showed diffuse infiltration by small lymphoid cells. (x40)
B: The malignant cells were partially stained CD20. (x40)
C: The malignant cells were positive CD5. (x40)
D: The malignant cells were focally positive CD23. (x40)

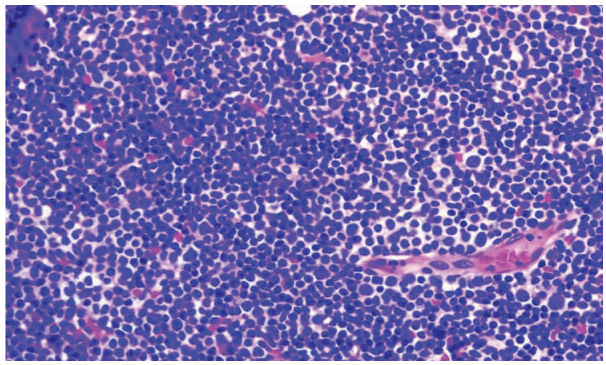

**Figure 4** Cervical lymph node biopsy showed diffuse infiltration by small lymphoid cells with proliferation center, no morphologic evidence of large cell transformation or plasmacytic differentiation. (x10)

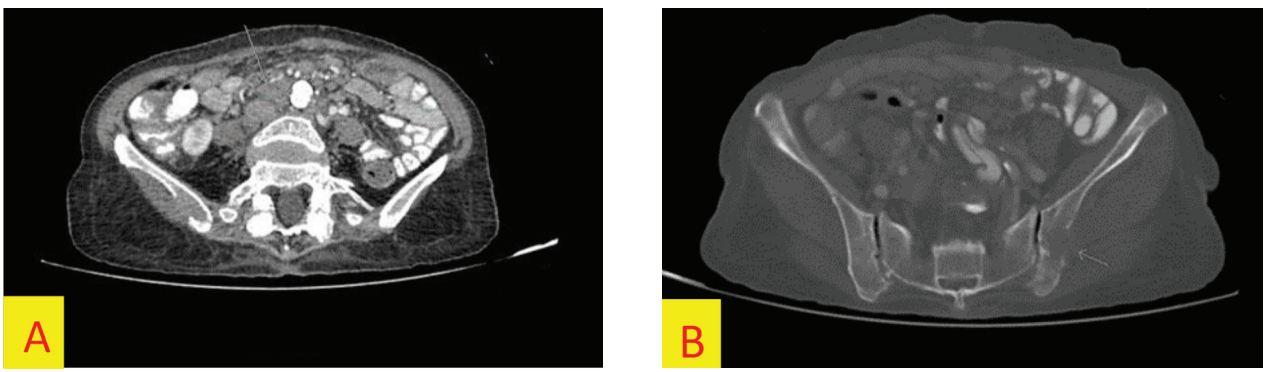


**Figure 5** CT scan of whole abdomen
A: Multiple para-aortic and mesenteric nodes at mid abdomen
B: Ill-defined osteolytic lesion at left iliac wing

## Discussion

Hypercalcemia is a common paraneoplastic symptom in solid cancers and in some lymphoproliferative disorder such as myeloma or T-cell leukemia-lymphoma. However, it is rarely reported in B cell CLL.[9] Several mechanisms leading to malignancy-related hypercalcemia include: [10-13]

1. Osteolytic hypercalcemia activates osteoclasts by either a primary bony tumor or metastases. Cytokine relates to hypercalcemia such as tumor necrosis factor-β (TNF-β), interleukin (IL)-1β, and IL-6.
2. Humoral hypercalcemia mediated by parathyroid hormone related peptide (PTHrP)
3. 1,25 dihydroxy vitamin D (calcitriol)

Osteolytic lesion is considered as a cause of hypercalcemia in this case as we found local osteolytic lesion at left iliac wing. Furthermore, other causes of hypercalcemia were not detected including an excess of 25-OH vitamin D level and a suppression of iPTH from malignancy mimicking PTHrP. We could not directly measure circulating PTHrP, TNF-α and IL-6 levels because these tests are unavailable in Thailand. Hypercalcemia in CLL is a rare condition and only nine cases were previously reported in literatures.[14]

CLL and multiple myeloma (MM) are both monoclonal hematologic malignancies of differentiated B-cells which are associated with hypercalcemia. Simultaneous occurrence of both diseases are uncommon. Only 11 patients diagnosed with both CLL and MM had been reported in a study from J.C. Broutet and colleagues.[15] It is difficult to distinguish between these conditions as their clinical features are similar. In this case,

the differential diagnosis of concomitant MM was proposed. This patient had features identical to MM including elderly, symptomatic hypercalcemia and developed acute kidney injury on top of chronic kidney disease. Bone marrow study was done and showed negative results for MM (normal plasma cells).

Solid tumors associated with hypercalcemia were also excluded in this case. Although the data of CLL concomitant with other solid tumors is lacking. CLL increases risk of developing some solid cancers including skin, lung and breast cancer with the median interval time of 53 months.[16] Our physical examinations and radiologic investigations is currently unremarkable. However, long-term follow-up is needed.

Hypercalcemia has been known to be associated with relapsed/refractory CLL or a severe condition, called Richter's syndrome.[12, 17-19] One of these report from J. Beaudreuil et.al. found 11% (34/304) of low-grade lymphoma that later developed Richter's transformation and four of them had symptomatic hypercalcemia. Half of these cases were diagnosed with an advanced stage CLL (Rai 3 or 4).[17]

None of previous studies reported symptomatic hypercalcemia as an initial presentation of CLL. J Eaudreuil et.al. found two CLL patients who progressed to Richter's syndrome and presented with symptomatic hypercalcemia. TNF-α levels were high whereas serum calcitriol levels were low in both cases. One case was checked for PTH level and that was suppressed. IL-6 was high in one case. The authors suggested that the increasing in TNF-α and IL-6 levels may correlate with hypercalcemia in terms of bone resorption. These circulating cytokines may interact synergistically with PTHrP to increase bone resorption.[17]

Hypercalcemia may correlate with an increased white blood cell count, lymph node enlargement and organomegaly among CLL patients.[20] A report showed relapsed-CLL patients with progression of hypercalcemia without evidence of Richter's syndrome.[9] These evidences suggested that hypercalcemia in CLL patient may imply high tumor burden or may develop Richter's syndrome. However, hypercalcemia is not indicated for a poor prognosis.[17]

General treatments of hypercalcemia in CLL are similar to the treatment for other causes of hypercalcemia. The treatments comprise of parenteral hydration with saline to promote calcinuria, and the administration of calcitonin and bisphosphonate to suppress bone resorption. Although general treatments of hypercalcemia could normalize calcium levels in most CLL cases, some studies showed little response until start chemotherapy.[18] In this case, we controlled serum calcium to normal range with hydrations and diuretics. Chlorambucil and prednisolone regimen was administered subsequently to this patient as it was a suitable treatment in the context of poor performance status and poor socioeconomic status. Serum calcium level remain normalized since the therapy was given.

## Conclusion

We report an interesting case of CLL who was initially presenting with symptomatic hypercalcemia, caused by osteolytic bone lesion. Hypercalcemia might indicate high tumor burden, relapsed disease or transformed into severe form (Richter's syndrome). Therefore, we recommended to closely monitor serum calcium levels during their indolent period.

## Acknowledgement

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