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Hypercalcemia presenting as the initial manifestation of Lymphoma

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ABSTRACT

Hypercalcemia as an initial presentation of malignant lymphoma is uncommon as many patients with lymphoma develop hypercalcemia late in the course of disease with extensive bone involvement. Also, among subgroups of lymphomas, hypercalcemia is more common in adult T cell lymphomas rather than B-cell lymphomas. We present a case of mature B cell lymphoma presenting as hypercalcemia in the absence of bone lesions. The case report discusses the pathogenesis, symptoms, and treatment of hypercalcemia.

Keywords: Non-Hodgkin's lymphoma, hypercalcemia, malignancy, B-cell lymphoma, T-cell lymphoma

INTRODUCTION

Hypercalcemia as the initial presentation of malignant lymphoma is uncommon. Most patients with lymphoma develop hypercalcemia late in the course of the disease and with extensive bone involvement.¹ Among the subgroups of lymphomas, hypercalcemia is more common in adult T cell lymphoma but rare in B cell lymphoma.² Most patients with lymphoma and hypercalcemia have extensive bone involvement.¹ Here we report a patient with mature B cell lymphoma presenting as hypercalcemia in the absence of any lytic bone lesions.

CASE REPORT

A 75-year-old Caucasian male was admitted to the hospital after found to have severe hypercalcemia. Two days before hospital admission, he presented to his primary care doctor with loss of appetite, unintentional weight loss, and fatigue. He denies any other symptoms of hypercalcemia (polyuria, polydipsia, constipation, bone pain, abdominal pain) or B symptoms of lymphoma. (fevers, night sweats, pruritus).

The patient was on calcium and vitamin D supplements for eight months before the current admission. Other medications include synthroid, simvastatin, and vitamin C supplements. Family

history significant for liver and lung cancer, affecting his siblings. He has 20 pack-year smoking history, stopped 30 years back.

On examination, the patient noted to have significant lymphadenopathy in the right inguinal, right, and left anterior cervical regions. On admission, serum calcium levels were found to be significantly elevated at 16 mg/dl, acute renal failure with creatinine 3.62 mg/dl, and BUN 47 mg/dl. CBC revealed new-onset anemia with hemoglobin if 9.8 g/dL. His other laboratory tests including white cell count, liver function, thyroid function, serum cortisol, Angiotensin-converting enzyme (ACE) level, serum immunoglobulins, Prostate-specific antigen (PSA), 25 hydroxy vitamin D levels, Alpha-fetoprotein, Carcinoembryonic antigen, Parathyroid hormone-related peptide (PTHrp), urinary calcium levels were all within normal limits. Serum protein electrophoresis with immunofixation, urine protein electrophoresis, and thyroid autoantibodies were all negative. Parathyroid hormone (PTH) was suppressed at <2.5 pg/ml, B2 microglobulin, and LDH were elevated at 11.6 mg/dl and 594 IU/l, respectively. Bone Scan and skeletal survey were unremarkable. Ultrasound of the renal system showed normal-sized kidneys and increased restrictive indices consistent with the renal parenchymal disease. Right inguinal lymph node biopsy revealed diffuse (mature) B cell lymphoma of follicular origin as shown in figure 1. Flow cytometry demonstrated an expansion of variably sized, predominantly small, surface lambda restricted CD5-, CD10+, CD19 +,CD20+, CD23-, CD38+ IgM+ B cells., consistent with mature diffuse large B cell lymphoma.

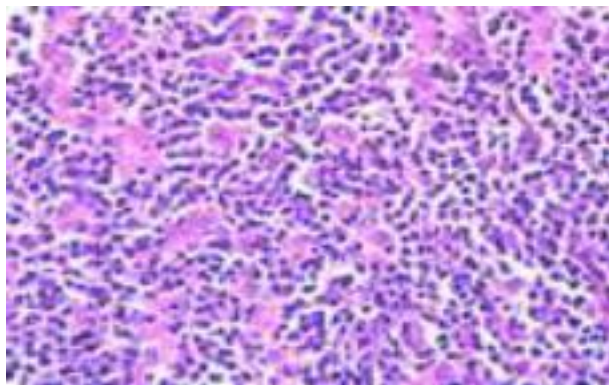


Figure 1 - Right inguinal lymph nodal biopsy specimen showing Diffuse B cell lymphoma of follicular origin.

He was treated with IV fluids, Pamidronate, calcitonin with the improvement of serum calcium and creatinine.

DISCUSSION

Hypercalcemia associated with lymphoma can be classified into four broad categories - Hypercalcemia due to tumor involvement of bone, Humoral hypercalcemia of malignancy, and Calcitriol induced hypercalcemia and Ectopic hyperparathyroidism.³ The categories of hypercalcemia associated with lymphoma is summarized in table 1.

Table 1. Types of Hypercalcemia Associated with Lymphoma

Type	Causal agent
Local osteolytic hypercalcemia	Cytokines, chemokines, PTHrp
Humoral hypercalcemia of malignancy	PTHrP
1,25 (OH) ₂ D- secreting lymphoma - most common	1,25 (OH) ₂ D
PTH - parathyroid hormone PTHrP - PTH related protein 1,25 (OH) ₂ D - 1,25-dihydroxy vitamin D	

Hypercalcemia due to local osteolysis of the involved bone is typically seen in advanced lymphoma and in primary lymphoma of bone resulting in hypercalcemia.^{1,4} Bone scans (scintigraphy) is a very sensitive study to identify osteoblastic lesions and skeletal survey to determine osteolytic lesions. In our patient local osteolysis is unlikely given normal skeletal survey.

Humoral hypercalcemia of malignancy is mediated by PTHrP, a distinct gene product with sequence homology to PTH only in a limited domain at the amino-terminal of the molecule.⁵ PTHrP produce hypercalcemia by increasing bone resorption throughout the skeleton and by increasing the renal resorption of calcium. PTHrP activates osteoblasts to produce Receptor activator of nuclear factor-kappa ligand (RANKL), in turn, activates osteoclast precursors and subsequent bone osteolysis leading to the release of bone-derived growth factors, including insulin growth factor 1 (IGF1) and transforming growth factor beta (TGF b). The growth factors bind to the surface receptors on tumor cells and activate both cytoplasmic mediators of TGF beta

and mitogen-activated protein kinase. Signaling through this pathway promotes both cancer cell proliferation and PTHrP production with subsequent further increase in calcium resorption.⁵ In our patient, PTHrP was not elevated, and therefore Humoral Hypercalcemia of Malignancy due to PTHrP is unlikely the explanation for his hypercalcemia. The pathophysiology of hypercalcemia is summarized in figure 2.

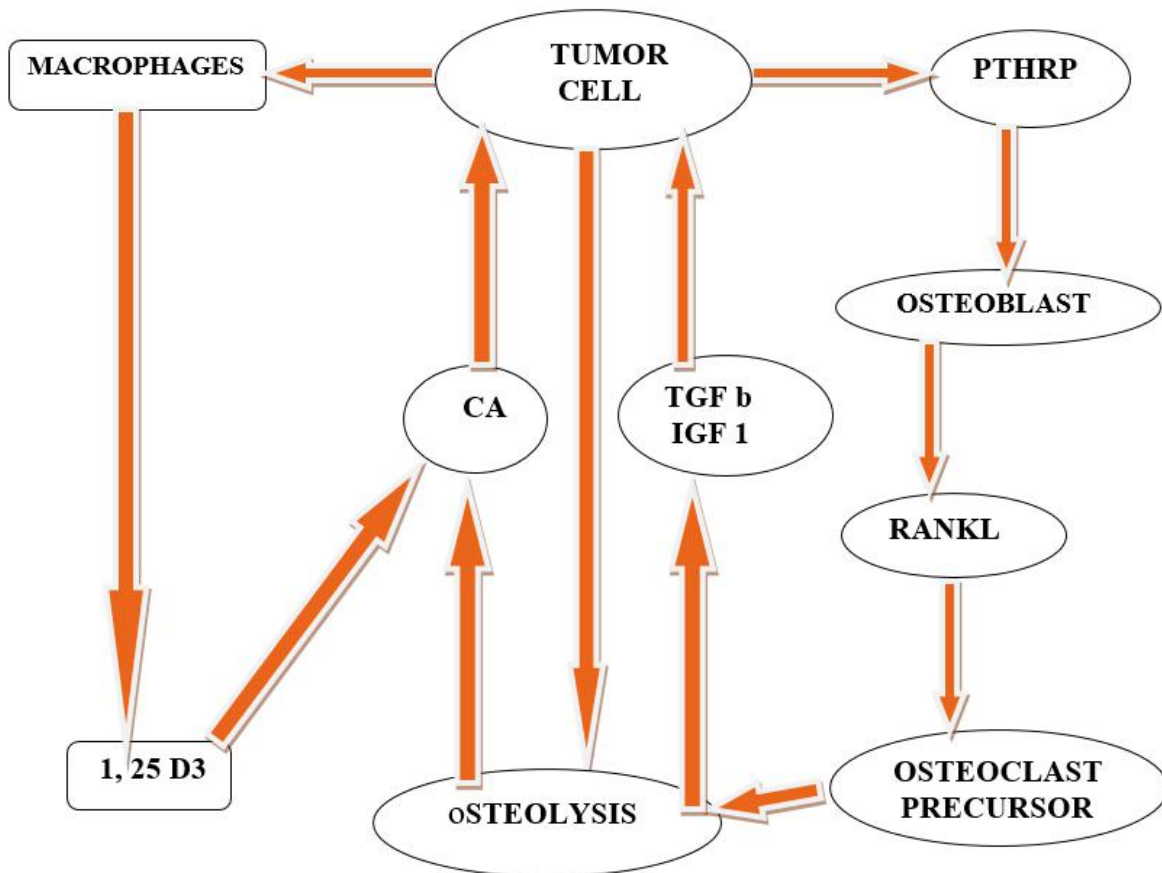


Figure 2 –Pathophysiology of hypercalcemia

CA- calcium

TGF b - transforming growth factor beta

IGF 1 - insulin growth factor I

RANKL - Receptor activator of nuclear factor-kappa ligand

PTHrP - parathyroid hormone related peptide

Hypercalcemia due to Calcitriol secretion is a common cause of hypercalcemia in lymphoma.⁶ Metabolism of Vitamin D, PTH, and calcium regulation is not fully understood. PTH and calcitriol regulate calcium levels. PTH is the primary trophic stimulator of renal one-alpha-

hydroxylase – the enzyme that converts 25 hydroxy calciferol into calcitriol. Calcitriol, in turn, inhibits PTH secretion by two different mechanisms – 1. Direct repression of pro-parathyroid gene 2. Inhibition of synthesis and release of PTH as an indirect consequence of hypercalcemia. In normal circumstances, the kidney is the primary source of circulating calcitriol. This is because the extrarenal one- alpha-hydroxylase is more sensitive to feedback inhibition than the renal one-alpha-hydroxylase alone. A notable exception to this rule is activated macrophages;² they lack the ability for feedback inhibition, likely the common etiology of hypercalcemia in Tcell lymphomas. The lymphomatous tissue will act as a source of calcitriol, which in turn increases the serum calcium level by increasing the calcium absorption. In our patient, however, the 1,25 Dihydroxy vitamin D3 levels were normal, and therefore this mechanism is unlikely to account for hypercalcemia.

In many cases of hypercalcemia and lymphoma, the cause is not very clear. In case series of 22 patients with non-Hodgkin's lymphoma (NHL), Seymour et al. report ten patients to have high calcium yet normal calcitriol levels.⁷ Thus calcitriol cannot be the only mediator of hypercalcemia in patients with lymphoma. There could be other cytokines involved in the mediation of hypercalcemia.

The clinical features of hypercalcemia can have a myriad of non-specific symptoms; gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and constipation are commonly experienced. Dehydration due to vomiting and polyuria in the setting of hypercalcemia can cause acute kidney injury.⁸⁻¹⁰ Neuropsychiatric changes can be seen in the form of fatigue, somnolence, lethargy, mood swings, and cognitive dysfunction.^{8 -10} Diagnostic evaluation should include ionized calcium and PTH levels. However, if ionized calcium levels are unavailable, then calcium and albumin levels should be measured at the same time with correction for albumin levels.

Treatment of the underlying malignancy is the most successful treatment strategy.⁸ Acute hypercalcemia is managed with intravenous fluids and frequent monitoring of calcium levels.⁸ Loop diuretics decrease calcium reabsorption and can be added after appropriate fluid resuscitation. Bisphosphonates can also be added due to their inhibitory effects on bone resorption.⁸ Calcitonin suppresses bone resorption and can be used in the acute setting.^{9,10} Denosumab binds to RANKL to prevent ligand interaction with RANK receptors on precursor

osteoclasts which interferes with osteoclast maturation and survival.¹¹ It prevents skeletal-related events in patients with bone metastases and is a generally well-tolerated treatment.¹² The pharmacological management of hypercalcemia is summarized in Table 2.

Table 2. Pharmacologic Therapy for Hypercalcemia with Cancer

Intervention	Dose
Hydration or Calciuresis	
Intravenous Saline	200 – 500 ml/hr, depending on the cardiovascular and renal status of the patient.
Furosemide	20 – 40 mg intravenously, after rehydration has been achieved
First-line medications - Intravenous Bisphosphonates	
Pamidronate	60 – 90 mg IV over a 2 hour period
Zoledronate	4 mg IV over a 15 min period
Denosumab (Anti Rankl Therapy)	120 mg subcutaneous once that is refractory to bisphosphonate therapy or patients with severe renal impairment
Promising Therapies	
Antibodies against PTHrp	Still in the clinical trial phase
Other therapies include Glucocorticoids, Mitramycin, Gallium nitrate, and Calcitonin	

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