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Stones, Bones, and Groans with Cancerous Overtones - A Rare Case of Diffuse Large B Cell Lymphoma Presenting as Hypercalcemia

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Abstract

Diffuse large B cell lymphoma (DLBCL) is a type of non-Hodgkin lymphoma that can present in a variety of ways including fever, weight loss, weakness, and drenching night sweats. Uncommonly, hypercalcemia of malignancy can be associated with DLBCL through multiple mechanisms that include synthesis of parathyroid hormone related peptide (PTHrP) or elevated calcitriol levels. It is estimated that hypercalcemia in the setting of DLBCL is present in 18% of newly diagnosed cases. This report details a case of an 80-year-old man with history of chronic anemia and CKD stage 3b that presented with weakness, decreased oral intake, and self-reported weight loss. Initial labs showed a corrected calcium of 14.1 mg/dL and normal phosphorous and alkaline phosphatase levels. PTH was decreased at 4 pg/mL. Serum protein electrophoresis and skeletal survey were unremarkable. A continued anemia of 8.1 g/dL in the setting of hypercalcemia prompted further investigation with endoscopy and colonoscopy which showed a large malignant-appearing mass in the mid gastric body. Pathology identified the mass as DLBCL germinal center type. Labs taken after endoscopy reported elevated 1,25-dihydroxyvitamin D levels, consistent with vitamin-D induced hypercalcemia seen in DLBCL. This case report highlights an uncommon yet important presentation of DLBCL. It is imperative that a differential diagnosis for undifferentiated hypercalcemia in an older patient should include malignancies such as DLBCL and workup should include extrarenal causes of hypercalcemia such as PTHrP production and calcitriol levels.

Keywords

DLBCL, Lymphoma, Hypercalcemia, Diffuse Large B Cell Lymphoma, PTHrP

Conflict of Interest Statement

No Conflict of Interest Exist

Cover Page Footnote

We would like to Acknowledge Katherine Chung, M.D. for providing Figure 1.

CASE REPORT

Stones, Bones, and Groans with Cancerous Overtones - A Rare Case of Diffuse Large B Cell Lymphoma Presenting as Hypercalcemia

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Abstract

Diffuse large B cell lymphoma (DLBCL) is a type of non-Hodgkin lymphoma that can present in a variety of ways including fever, weight loss, weakness, and drenching night sweats. Uncommonly, hypercalcemia of malignancy can be associated with DLBCL through multiple mechanisms that include synthesis of parathyroid hormone related peptide (PTHrP) or elevated calcitriol levels. It is estimated that hypercalcemia in the setting of DLBCL is present in 18% of newly diagnosed cases. This report details a case of an 80-year-old man with history of chronic anemia and CKD stage 3b that presented with weakness, decreased oral intake, and self-reported weight loss. Initial labs showed a corrected calcium of 14.1 mg/dL and normal phosphorous and alkaline phosphatase levels. PTH was decreased at 4 pg/mL. Serum protein electrophoresis and skeletal survey were unremarkable. A continued anemia of 8.1 g/dL in the setting of hypercalcemia prompted further investigation with endoscopy and colonoscopy which showed a large malignant-appearing mass in the mid gastric body. Pathology identified the mass as DLBCL germinal center type. Labs taken after endoscopy reported elevated 1,25-dihydroxyvitamin D levels, consistent with vitamin-D induced hypercalcemia seen in DLBCL. This case report highlights an uncommon yet important presentation of DLBCL. It is imperative that a differential diagnosis for undifferentiated hypercalcemia in an older patient should include malignancies such as DLBCL and workup should include extrarenal causes of hypercalcemia such as PTHrP production and calcitriol levels.

Keywords: DLBCL, Lymphoma, Hypercalcemia, Diffuse large B cell lymphoma, PTHrP

1. Background

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and represents 40% of all cases with a 66% cure rate.[1] It is more common in men and older adults with the mean age of diagnosis being 64 years. Similar to other cancers, DLBCL usually presents as a fast, non-painful, growing mass in the neck, abdomen or groin and can be associated with B symptoms such as fever, weight loss, weakness, and drenching night sweats.[1] Hypercalcemia of malignancy is commonly associated with cancers such as multiple myeloma, squamous cell, and ovarian cancers. It is important to note that while rare, diffuse large B cell lymphoma can also be associated with hypercalcemia. One proposed mechanism includes the synthesis of PTH-Related Peptide (PTHrP) by cancerous lymph nodes which then induces osteolysis via osteoclasts and subsequently hypercalcemia.[2] This process is exacerbated by TGF-B cells which further induce tumor cell differentiation leading to even more PTHrP production (Fig. 1). Another factor that can cause hypercalcemia in DLBCL is elevated serum levels of 1,25-dihydroxycholecalciferol (calcitriol). Calcitriol, or activated vitamin D, functions to facilitate the intestinal absorption of calcium[3] (Fig. 1). Without proper feedback mechanisms, uncontrolled activation of vitamin D can inappropriately elevate

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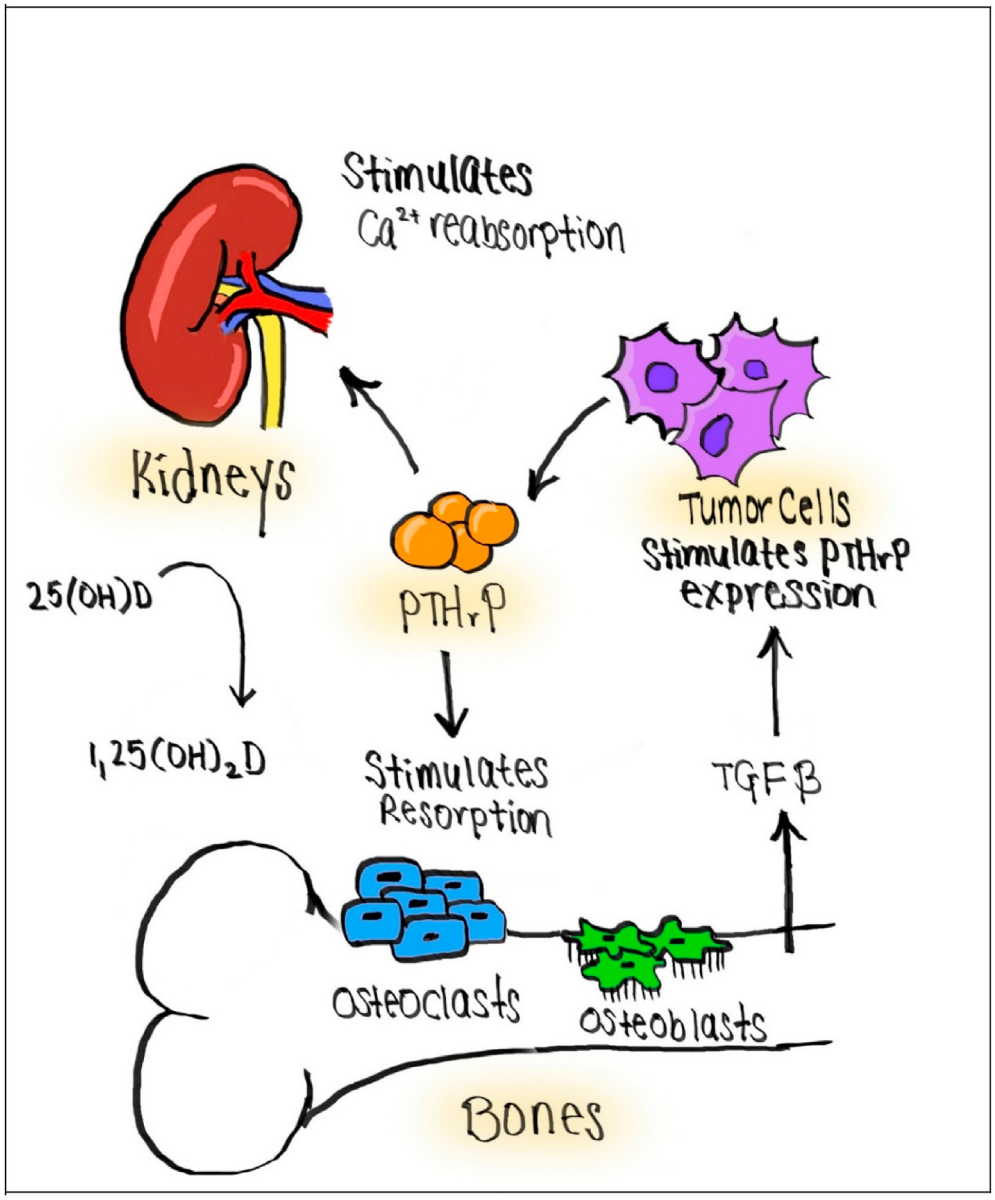

Fig. 1. Expression of PTHrP leading to Hypercalcemia. Image provided by Katherine Chung, M.D.

calcium levels. Here we describe an uncommon phenomenon of hypercalcemia in the setting of DLBCL which can be present in up to 18% of new diagnoses.[4]

2. Objective

Recognize the role of hypercalcemia in DLBCL and its associated prognosis.

3. Case report

An 80-year-old male non-smoker with a past medical history of chronic anemia and CKD stage 3b presented to the ED after an unwitnessed fall with associated weakness and decreased oral intake for two weeks duration. Associated history included decreased appetite with self-reported weight loss but no fever, nausea, or night sweats. Physical exam was remarkable for a 2 cm palpable mass in the mid-epigastric region. Initial workup was significant for creatinine of 2.18 mg/dL, calcium of 13.3 mg/dL and albumin of 3.0 g/dL, which resulted in corrected calcium of 14.1 mg/dL, with normal phosphorus and alkaline phosphatase levels. Upon further testing, PTH was decreased at 4 pg/mL and a 25-hydroxyvitamin D level of 23 ng/mL which was consistent

with his baseline. These lab results in conjunction with the patients' demographics were concerning for multiple myeloma or a PTHrP-induced hypercalcemia of malignancy. Further workup was sent including urine and serum protein electrophoresis and a skeletal survey which were all unremarkable. Kappa/lambda ratio was elevated at 5.40, though nonspecific. Chest CT showed moderate bilateral pleural effusions suspicious for cancer. Given that multiple myeloma and lung cancer appeared less likely at this point and an ongoing severe anemia with Hgb of 8.1 g/dL, an upper endoscopy and colonoscopy were performed which showed a large malignant-appearing mass in the mid-gastric body. Pathology reports showed diffuse large B cell lymphoma, germinal center type that was CD20, BCL6, and c-Myc positive. In addition, labs later showed a normal PTHrP level and an elevated 1,25-dihydroxyvitamin D level at 117 pg/mL, consistent with vitamin-D induced hypercalcemia seen in DLBCL. After discussing goals of care, the patient decided to be placed on Hospice and passed away a short time later.

4. Discussion

DLBCL is the most common type of non-Hodgkin lymphoma and is very aggressive. Without treatment, the median survival rate is only several months. In those who present with lymphoma-related hypercalcemia it is associated with a more advanced stage, shorter progression-free-survival, and overall survival.[1] Similar to the case above, lymphomas with calcitriol related hypercalcemia are linked to worse outcomes such as decreased progression-free survival which suggest that it might be a marker of high-grade lymphoma or even a presenting sign of cancer recurrence.[3] Furthermore, this report describes a case of hypercalcemia in DLBCL germinal center type, which is even less common than hypercalcemia in non-germinal center type. Fortunately, with treatment using R−CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), almost all patients respond, and 50−70% are cured.[5] Therefore, a differential diagnosis for undifferentiated hypercalcemia in an older patient should include DLBCL and other malignancies. Also, lab workup should evaluate for elevated PTHrP and/or calcitriol to determine prognosis.

Conflict of interest

The authors state that no conflict of interest exists.

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