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CASE REPORT

Hypercalcemia in non-Hodgkin's lymphoma due to cosecretion of PTHrP and 1,25-dihydroxyvitamin D

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Abstract

Hypercalcemia occurs in up to 30% of patients with malignancies and can be due to osteolysis by metastases, parathyroid hormone-related protein (PTHrP), excess 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) production or, rarely, ectopic parathyroid hormone (PTH) secretion. Hypercalcemia in non-Hodgkin's lymphoma has been described with elevations in PTHrP or, more commonly, excess $1,25(OH)_2D$ production. We present the first case of a patient with new diagnosis of non-Hodgkin's lymphoma and severe hypercalcemia who was found to have concurrently elevated PTHrP and $1,25(OH)_2D$. In human studies, PTHrP has shown limited ability to stimulate $1,25(OH)_2D$ production. To demonstrate that both PTHrP and $1,25(OH)_2D$ were of tumor origin in our patient, tissue from her tumor underwent histochemical staining, demonstrating expression of both PTHrP and CYP27B1, indicating the presence of $1,25(OH)_2D$ production in the tumor tissue. Our case illustrates the complexity of hypercalcemia in patients with underlying malignancy and highlights the importance of a thorough diagnostic workup for achievement of a successful therapeutic approach. In our patient, definitive chemotherapeutic treatment resulted in achievement and maintenance of normal calcium, PTHrP and $1,25(OH)_2D$ levels 18 months after initial diagnosis.

Summary

Hypercalcemia occurs in up to 30% of malignancies and can be due to several mechanisms. We present the first case of cosecretion of parathyroid hormone related peptide (PTHrP) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) in a patient with non-Hodgkin's lymphoma and demonstrate that both PTHrP and $1,25(OH)_2D$ were of tumor origin by immunohistochemical staining.

Keywords hypercalcemia, · malignancy, · 1,25-dihydroxyvitamin D, · PTHrP

Introduction

Hypercalcemia in patients with malignancy is relatively common, occurring in up to 20–30% of cases [1] and is associated with a poor prognosis [2]. Several mechanisms for hypercalcemia of malignancy have been described: osteolysis by local metastasis, parathyroid hormone-related protein (PTHrP) mediated, increased 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) production or, in rare cases, ectopic parathyroid hormone (PTH) secretion.

Increased bone resorption by osteolytic metastasis through osteoclastogenic factors is most commonly seen with solid tumors metastasized to bone [3], multiple myeloma [4] and is rarely encountered in hematologic malignancies. PTHrP-mediated hypercalcemia, also known as humoral hypercalcemia of malignancy (HHM), is most commonly encountered in patients with solid cancers metastasized to bone such as squamous cell carcinomas, breast, renal or bladder carcinomas and hematologic malignancies like T cell leukemia/lymphoma and non-Hodgkin's lymphoma (NHL) [5]. PTHrP and PTH peptides have similar actions on the kidney and bone including

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increased bone resorption, renal phosphorus excretions, and distal tubular calcium reabsorption. They differ in their effects on serum $1,25(OH)_2D$. PTHrP is a less effective stimulator of the renal CYP27B1 in humans [6] and serum $1,25(OH)_2D$ levels are usually suppressed in HHM.

Excessive production of $1,25(OH)_2D$ is commonly seen in Hodgkin's and NHL [7], and squamous cell carcinomas, but rarely in solid tumors such as ovarian dysgerminoma [8], pancreatic neuroendocrine tumors [9], or bronchogenic carcinoma [10]. Although PTHrP and excess $1,25(OH)_2D$ can independently cause hypercalcemia in patients with NHL, the simultaneous presence of both has not previously been reported. Here, we present a case of NHL and hypercalcemia due to concomitant production of PTHrP and $1,25(OH)_2D$.

Case presentation

A 53-year-old female with a history of renal transplantation for idiopathic glomerulonephritis was referred to the Emergency Department after outpatient laboratory evaluation revealed a serum calcium level of 18 mg/dl. Two weeks prior, she had presented to her primary care physician with mild fatigue and constipation. Serum calcium at that time was 12.1 mg/dl, albumin 4.1 mg/dl, and creatinine 1.2 mg/dl. Calcium and vitamin D supplements were discontinued, and the patient was advised to return for laboratory testing 2 weeks later. Serum calcium level was normal on multiple occasions during the previous year.

Medical history included idiopathic glomerulonephritis resulting in end stage renal disease, renal transplantation 15 years prior, on chronic immunotherapy. Additionally, the patient had a history of tertiary hyperparathyroidism status post partial parathyroidectomy 16 years prior with subsequent normal serum PTH and calcium levels, osteopenia previously treated with oral bisphosphonate for six years, basal cell skin cancer, and hypertension. On initial physical examination, the patient was hypertensive, BP 180/75 mmHg, but in no acute distress. Cervical lymphadenopathy was palpated. Findings from neurologic, cardiovascular, and musculoskeletal examinations were otherwise unremarkable.

Laboratory evaluation revealed serum total calcium level of 18 mg/dl, ionized calcium > 4.2 mmol/L, albumin 4.0 mg/dL, low magnesium level of 1.2 mEq/L, phosphorus of 3 mg/dL, elevated BUN at 36 mg/dL, creatinine 2 mg/dL (baseline 1.2 mg/dL), and decreased GFR at 26 mL/min/A, (A =1.73 sq m). Additional laboratory evaluation revealed elevated alanine amino transferase level of 96 U/L, aspartate amino transferase level of 149 U/L, low sodium level of 127 mEq/L, and elevated potassium of 5.8 mEq/L (Table 1). The red blood cell, platelet, and white blood cell counts were normal with immature granulocytes (promyelocytes, myleocytes, and metamyelocytes) detected.

Evaluation of hypercalcemia revealed intact PTH level of 11 pg/mL, 25-hydroxyvitamin D (25OHD) level of 23 ng/mL, elevated PTHrP of 84 pg/mL (normal range 14–27), elevated $1,25(OH)_2D$ of 140 pg/mL (normal range 18–72 pg/mL), LDH 546 U/L, TSH 0.51 mcIU/mL, normal serum and urine electrophoresis, normal CEA, CA 19-9 and elevated CA-125 level of 476 U/mL. Evaluation for infectious causes was negative. Thoracic, abdominal, and pelvic computed tomography (CT) revealed mediastinal, cardiophrenic angle and internal mammary lymphadenopathy, diffuse mesenteric and omental induration and nodularity as well as moderate size right pleural effusion. Positron emission tomography-CT (PET-CT) demonstrated diffuse omental/peritoneal caking, hypermetabolic retroperitoneal, intrathoracic, left supraclavicular and axillary nodes. Additionally, a solitary hypermetabolic osseous lesion in the 5th rib and enlarged left ovary measuring 3.2 × 5.2 cm on the transverse projection were noted.

The patient underwent fine needle aspiration of the left supraclavicular lymph node, excision of three left cervical lymph nodes as well as bone marrow aspiration and biopsy. Surgical pathology of the excised lymph nodes showed aggressive diffuse large B-cell lymphoma with 77% monoclonal, lambda-restricted B cells identified on flow cytometry. Immunohistochemical stains showed that the neoplastic cells were positive for CD20, BCL-2, and BCL-6 and negative for MUM-1, CD138, HHV-8, and CD3. The Ki-67 proliferation index was >95%. In situ hybridization for Epstein-Barr virus-encoded RNA (EBER) was negative. The marrow was normocellular with trilineage hematopoiesis present and full range of maturation with no evidence of lymphoma. Immunohistochemical staining (IHC) was performed on the sections of the excised lymph node using antibodies against CYP27B1 and PTHrP. As shown in Fig. 1, strong expression of CYP27B1 (Fig. 1B) and PTHrP (Fig. 1C) were demonstrated by serial lymphoma sections. In contrast, neither CYP27B1 nor PTHrP expression was observed in diffuse large lymphocytes (Fig. 1D and F) and reactive lymph node (Fig. 1 E and G) sections.

The patient received aggressive intravenous fluid hydration, calcitonin 200 units every 12 h, and one dose zoledronic acid 4 mg. Calcium remained elevated at 12.5 mg/dl. Intravenous solumedrol followed by chemotherapy with R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) was initiated. Five additional cycles followed over the next 5 months.

The patient's serum calcium decreased to 9.6 mg/dl, albumin 2.7 mg/dl on the day of discharge. PET-CT obtained 1 and 2 months post discharge revealed resolution of previously seen adenopathy, normal ovaries, with no residual hypermetabolic disease. On the last follow-up, 18 months later, her serum calcium, $1,25(OH)_2D$, and PTHrP levels were normal (Table 1).

Table 1 Laboratory measurement at presentation of hypercalcemia and on follow-up after treatment for non-Hodgkin's lymphoma. *LDH* lactate dehydrogenase, *PTH* parathyroid hormone, *25OHD* 25-hydroxyvitamin D, *1,25(OH)$_2$D* 1,25-dihydroxyvitamin D, *PTHrP* parathyroid hormone-related peptide

Laboratory parameter	On presentation	Follow-up	Reference range
Calcium (mg/dL)	18	9.2	8.4–10.5
Calcium ionized (mmol/L)	>4.2	N/A	1.13–1.32
Phosphorus (mg/dL)	3	3.4	2.7–4.5
Magnesium (mg/dL)	1.2	N/A	1.6–2.4
Albumin (mg/dL)	4	3.6	3.5–5.3
ALT (U/L)	96	14	0–31
AST (U/L)	149	21	0–31
Alkaline phosphatase (U/L)	76	51	30–120
Creatinine (mg/dL)	2	1	0.5–1.2
BUN (mg/dL)	36	19	7–22
eGFR (ml/min/A)	26	58	>60
LDH (U/L)	546	149	122–220
PTH (pg/mL)	11	59	10–65
25OHD (ng/mL)	23	42	30–100
1,25(OH)$_2$D (pg/mL)	140	35	18–72
PTHrP (pg/mL)	84	12	14–27

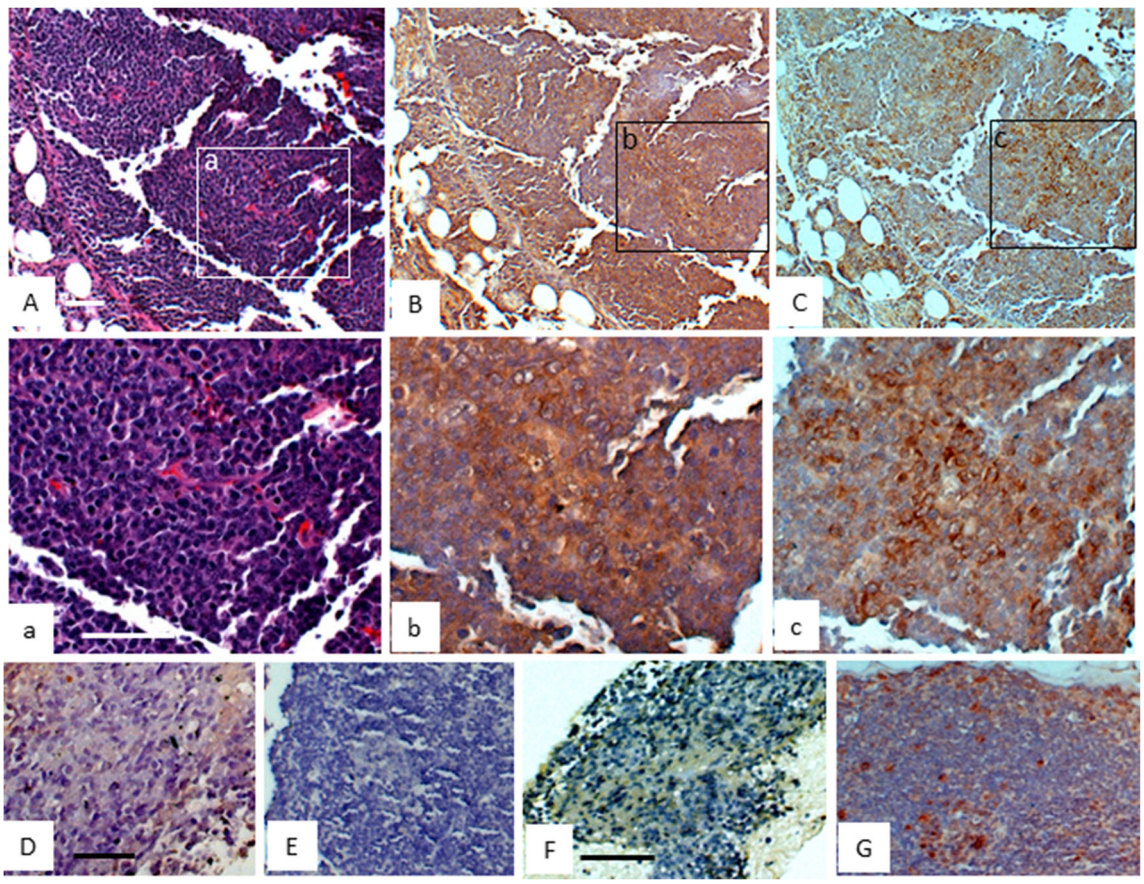

Fig. 1 The expression of CYP27B1 and PTHrP in lymphoma and control lymph node. A: H & E staining showed morphology of lymphoma. B–C: Immunohistochemistry staining (IHC) identified the expression of CYP27B1 (brown, B) and PTHrP (brown, C) in the serial lymphoma sections to A. a–c High magnification images of the framed areas in A–C. D–E: IHC revealed that no CYP27B1 (D–E) and PTHrP (F–G, slight background in the fibrous tissue) in diffuse large lymphocytes (D and F) and reactive lymph node (E and G) sections. 10 × in A–C, 20 × in a–c, and D–G. bars = 50 μm

Methods

CYP27B1 and PTHrP expression were determined by immunohistochemistry using goat CYP27B1 antibody (1:50) or rabbit PTHrP antibody (1:100) in paraffin-embedded sections and were detected with biotinylated secondary antibodies, followed by ABC peroxidase reagent. All antibodies were obtained from Santa Cruz Biotechnology, Inc., Santa Cruz, CA. The expression was visualized by diaminobenzidine substrate and hematoxylin counterstaining.

Discussion

Our case highlights the importance of a thorough diagnostic work-up of hypercalcemia in patients with underlying malignancy for successful treatment of this challenging condition. Hypercalcemia in patients with hematologic malignancies has been well reported in the literature. Several underlying mechanisms have been described. In a prospective study of 165 consecutive patients with malignant hematologic malignancies, the incidence of hypercalcemia was 10.9%, with primary hyperparathyroidism accounting for only 1.8% of cases. The vast majority of cases involved the lymphoid lineage (multiple myeloma and NHL) with either PTHrP or excess $1,25(OH)_2D$ as the humoral mediators [5].

PTH and PTHrP share several structural similarities explaining their homologous actions on bone and kidney. Both peptides stimulate osteoclastic bone resorption, and enhance renal tubular calcium reabsorption and phosphate excretion, resulting in elevated serum calcium and lower phosphorus concentration [11, 12]. However, PTHrP has limited stimulatory effect on 1-α-hydroxylase activity in the kidney and the $1,25(OH)_2D$ concentrations typically are normal or suppressed in patients with HHM [13].

In contrast with animal studies where PTHrP stimulates $1,25(OH)_2D$ production [14], studies in humans have shown limited effects and only at higher concentrations. Continuous infusions of different concentrations of PTH and PTHrP differed in their effects on $1,25(OH)_2D$. As expected, the $1,25(OH)_2D$ increased proportional with escalating doses of PTH. PTHrP at low and medium doses produced no change in serum $1,25(OH)_2D$ levels, while a modest increase was seen with the highest PTHrP concentration. Although the exact explanation for these discordant effects is not clearly known, one hypothesis is that more prolonged exposure of the kidney to PTHrP as in HHM results in down regulation of PTHrP response with decline in $1,25(OH)_2D$ [6].

Although the exact underlying mechanism responsible for the $1,25(OH)_2D$ suppression in the presence of elevated PTHrP remains largely unknown, several potential explanations have been proposed. Direct suppression of 1-α-hydroxylase activity by the elevated serum calcium concentration or indirectly by calcium induced suppression of PTH secretion, impaired renal function due to hypercalcemia or species differences in hydroxylase responsiveness to PTHrP are proposed mechanisms [15]. The concept of 1α-hydroxylase activity inhibition by hypercalcemia is supported by the rise in PTH and $1,25(OH)_2D$ level after normalization of serum calcium despite persistently elevated PTHrP levels [16]. Production of additional factors from tumor cells completely distinct from PTHrP may be responsible for direct suppression of renal $1,25(OH)_2D$ production as proposed by other authors [17]. Another potential explanation is that the two peptides exert different regulatory action on 1-α-hydroxylase through different signaling pathways [6].

The exact mechanism responsible for hypercalcemia in a patient with NHL is not clearly defined but excess $1,25(OH)_2D$ production has most commonly been reported, with PTHrP less frequently detected in these patients [18]. In a recent review of 17 patients with NHL and hypercalcemia, 61.1% of patients had neither PTHrP nor $1,25(OH)_2D$ elevations, 27.7% had elevated 1,25(OH)2D levels, and only 2 patients (11.2%) had isolated PTHrP elevation. No patient had elevations of both values. An interesting finding was the association between $1,25(OH)_2D$ mediated hypercalcemia and worse disease outcomes [19]. The site of malignant $1,25(OH)_2D$ production still remains a topic of debate. Normally, the 1-α-hydroxylase in the kidney converts the 25OHD to $1,25(OH)_2D$ under the physiologic control of PTH. Hypercalcemia results in suppression of PTH release and therefore lowers $1,25(OH)_2D$ production. Both cancer cells [20] and neighboring macrophages [21] have been described as potential sources of excess $1,25(OH)_2D$ production. Increased intestinal calcium absorption and stimulation of bone resorption are the mechanisms responsible for hypercalcemia in patients with $1,25(OH)_2D$ mediated hypercalcemia, while PTH and PTHrP are usually suppressed.

An unexpected finding in our patient was the concomitant elevation in plasma PTHrP and $1,25(OH)_2D$. To our knowledge this represents a unique case of NHL where elevated levels of both factors has been reported. Hypercalcemia with simultaneous elevation in $1,25(OH)_2D$ and PTHrP has previously been described in the literature, although the number of case reports is limited and no previous reports were in patients with NHL. Ovarian cancer [22], seminoma [23], renal cell carcinoma [24], pancreatic neuroendocrine tumor [25], adult T cell leukemia-lymphoma [26], and non-small cell lung cancer [27] are cases where elevated levels of PTHrP and $1,25(OH)_2D$ have been described. However, the sources of these hormones were not determined, and whether both hormones originated in the tumor was not demonstrated.

In this study, we provide both biochemical as well as immunohistochemical data that the tumor was responsible for both the increase in PTHrP and $1,25(OH)_2D$ (Fig. 1). This raises the interesting possibility that the PTHrP produced by

the tumor was acting as an autocrine/paracrine factor to promote the production of $1,25(OH)_2D$ in the same cell also expressing the CYP27B1. Thus to our knowledge this is the first case of a tumor presenting with hypercalcemia due to elevations in both PTHrP and $1,25(OH)_2D$ production from the same cells demonstrated both biochemically and by immunostaining.

Our case illustrates the complexity of hypercalcemia in patients with underlying malignancy and highlights the importance of a thorough diagnostic work-up for achievement of a successful therapeutic approach. In our patient, definitive chemotherapeutic treatment resulted in achievement and maintenance of normal calcium, PTHrP and $1,25(OH)_2D$ levels 18 months after initial diagnosis.

Declarations

Conflict of interest None.

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