

# Hypercalcemia: A complicated puzzle

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## ABSTRACT

This is a mini-review concerning hypercalcemia of malignancy that represents a challenging condition requiring rapid management, not only in relationship with short term complications, but also with long term mortality concerning the originating tumor approach (if feasible). Hypercalcemia on a patient with previously known or unknown cancer may be caused by dehydration, concurrent medication causing increased serum calcium levels, concomitant primary or renal hyperparathyroidism, over production of vitamin D (which may be tumor-related) or by specific circumstances that induce suppression of parathormone (PTH), so called PTH-independent mechanisms. Specific circumstances related to an active cancer means an ectopic production of parathormone, metastasis causing osteolytic lesions, tumors that produce PTHrP (parathormone related peptide) and abnormal production of 1,25-dihydroxyvitamin D by a hematologic malignancy. Parathyroid carcinoma induces an excess of PTH which is caused by a malignancy but it is not a PTH independent entity. Once a malignancy-related hypercalcemia is identified based on biological panel (mostly blood assays), the investigations are essentially continued with different imaging techniques depending on signs (if any), accessibility, etc. The approach is based on a multidisciplinary panel, on one hand, in order to restore normal levels of calcium, on the other hand, to rapidly address the underlying cause. This is essential to contribute to the outcome which typically is poor.

**Keywords:** calcium, parathormone, hypercalcemia, renal tumor, parathyroid gland, malignancy-related hypercalcemia

## INTRODUCTION

Hypercalcemia of malignancy represents a challenging condition that requires rapid management, not only in relationship with short term complications, but also with long term mortality concerning the originating tumor approach (if feasible) (1,2).

## AIM

Our purpose is to point out several aspects of hypercalcemia with normal parathormone levels.

## METHOD

This is a mini-review. A few examples are provided based on authors' daily experience.

## MECHANISMS OF HYPERCALCEMIA

Hypercalcemia on a patient with previously known or unknown cancer may be caused by dehydration, concurrent medication causing increased serum calcium levels, concomitant primary or renal hyperparathyroidism, over production of vita-

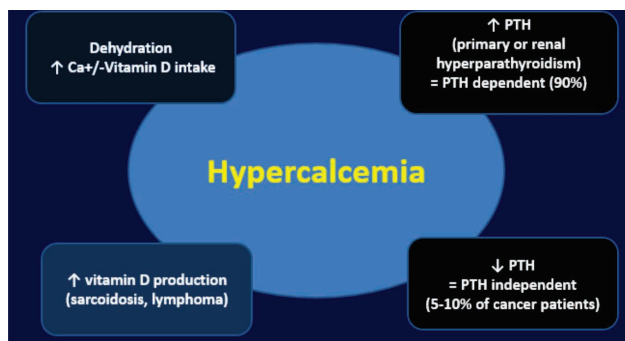


FIGURE 1. General mechanisms of hypercalcemia

min D (which is tumor-related) or by specific circumstances that induce suppression of parathormone (PTH), so called PTH independent mechanisms (3,4) (Figure 1).

Specific circumstances related to an active cancer means an ectopic production of parathormone, metastasis causing osteolytic lesions, tumors that produce PTHrP (parathormone related peptide) and abnormal production of 1,25-dihydroxyvitamin D by a hematologic malignancy (5,6). Parathyroid carcinoma induces an excess of PTH which is caused by a malignancy but it is not PTH-independent (7,8).

**ASSESSMENTS – BIOCHEMISTRY AND ENDOCRINE PANEL**

The combination of high calcium and reduced PTH is very suggestive for a PTH-independent mechanism which is activated by an active cancer in majority of situations (9,10) (Table 1).

TABLE 1. Panel of investigations of a 57-year old female with hypercalcemia due to a prior unknown renal malignancy. She had a tendency to weight loss since last few months; that is why she was investigated based on a routine biochemistry panel which detected high serum calcium and required more assays of calcium metabolism

Parameter	Value	Normal	Units
total serum calcium	12.3	8.4-10.2	mg/dl
Serum phosphorus	3.2	2.3-4.7	mg/dl
25OHD (25-hydroxyvitamin D)	24	>30	ng/ml
PTH (parathormone)	6	16-65	pg/ml
CrossLaps (bone resorption marker)	1.03	0.33-0.782	ng/ml
Osteocalcin (bone formation marker)	30	15-46	ng/ml
P1NP (bone formation marker)	40	15-58	ng/ml
alkaline phosphatase (bone formation marker)	171	38-105	U/l

**ASSESSMENTS – IMAGING PANEL**

Once a malignancy – related hypercalcemia is identified based on biological panel (mostly blood assays), the investigations are essentially continued with different imaging techniques depending on signs (if any), accessibility, etc., for instance, computed tomography, resonance magnetic imaging in addition to screening of different tumor markers (11,12) (Figure 2). Other investigations are bone scintigraphy, OctreoScan (somatostatin receptor scintigraphy), PET-CT, Ga-DOTATATE, DOPA PET etc. (11,13).

**MANAGEMENT OF HYPERCALCEMIA & ORIGINATING MALIGNANCY**

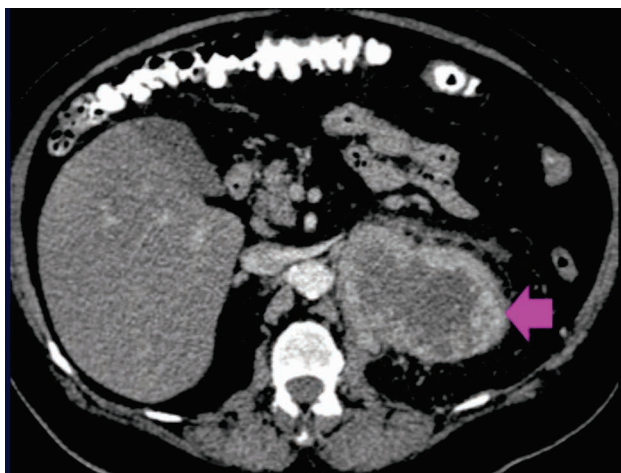
The approach is based on a multidisciplinary panel, on one hand, in order to restore normal levels of calcium, on the other hand, to rapidly address the underlying cause (14,15). The first purpose is approached based on reduction of calcium intake, increased fluids intake, control of medication like thiazides, excess of vitamin D in addition to bisphosphonates or denosumab and/or cinacalcet (16,17). The removal of primary tumor also improves the calcium levels as well as the overall prognostic (18,19).

**OUTCOME**

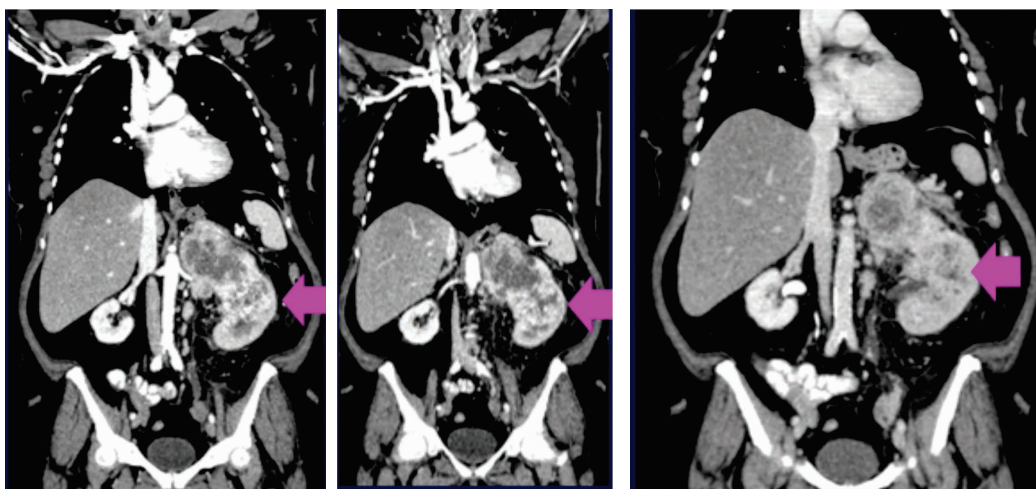
Malignancy-related hypercalcemia identification (which is frequently found in mammary and lung cancer), as part of endocrine paraneoplastic syndrome (EPNS) may be done before tumor diagnosis (as the first sign of the condition) or in patients with a long history of cancer; typically is has a poor prognostic (except for some types of breast cancers and neuroendocrine neoplasia) and it usually is associated with a 2-12 months survival (20,21,22).

**CONCLUSION**

The rapidity of recognition an entity like malignancy-related hypercalcemia is essential to identify previously unknown tumors; however, the condition is typically related to a poor outcome.



2A. Transverse plane at different sections



2B. Coronal plane at different sections

**FIGURE 2.** Intravenous contrast computed tomography (CT) scan showing a large left retroperitoneal tumor (involving the kidney and adrenal) with infiltrative contour and associated lymph nodes involvement with maximum diameter of 1.7 cm. The tumor has an axial diameter of 10.65 by 7.6 cm and a coronal (reconstruction) diameter of 8.61/13.53 cm

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