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Case Presentation

Non-Parathyroid Hyperparathyroidism: Rare Paraneoplastic Manifestation of GI Malignancy: A Case Report

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Abstract

Hypercalcemia is a frequent metabolic complication in malignancy, but the mechanisms are typically mediated through parathyroid hormone–related peptide (PTHrP), calcitriol production, or osteolytic metastases. True ectopic secretion of intact parathyroid hormone (PTH) by non-parathyroid tumors is exceedingly rare, with only a few cases documented in the literature. We present the case of a 73-year-old female with chronic kidney disease, hypertension, diabetes mellitus, and heart failure who presented in the ED with progressive altered mental status. Her laboratory evaluation revealed persistent hypercalcemia with elevated intact PTH levels. A parathyroid nuclear scan excluded primary hyperparathyroidism, while further workup ruled out PTHrP-mediated, vitamin D - related, and osteolytic causes. Her imaging revealed a retroperitoneal mass, and biopsy confirmed metastatic gastrointestinal adenocarcinoma. Considering the biochemical profile and negative parathyroid imaging, ectopic secretion of intact PTH from the malignancy was strongly suspected. Unfortunately, further confirmatory testing could not be performed due to her transition to the hospice. This case report highlights the diagnostic challenges posed by ectopic PTH production, a rare paraneoplastic manifestation, and also emphasises the importance of considering this rare etiology in patients with unexplained hypercalcemia and elevated PTH levels despite a negative parathyroid evaluation. Early recognition may enable timely management and prevent prolonged morbidity.

Introduction

Hyperparathyroidism is a metabolic derangement characterized by increased production of parathyroid hormone. Serum calcium may be decreased, increased, or normal, depending on renal function and other factors. In primary hyperparathyroidism, excess parathyroid hormone originates in adenoma, hyperplasia, or carcinoma of the parathyroid glands. Serum calcium levels are characteristically increased, although occasional patients may be normocalcemic. Parathyroid hormone (PTH) increases blood calcium levels through three main mechanisms. It stimulates bone resorption, releasing calcium into circulation, and increases renal reabsorption of calcium while promoting phosphate excretion. PTH also activates vitamin D in the kidney, which enhances intestinal absorption of calcium. Typically, serum phosphate levels are decreased. Secondary hyperparathyroidism is an adaptive increase in parathyroid hormone production induced most commonly by the hypocalcemia and hyperphosphatemia of chronic renal failure. Tertiary hyperparathyroidism refers to the development of autonomous parathyroid hyperfunction in patients with secondary hyperparathyroidism [1].

In primary hyperparathyroidism, the physical examination is often normal, though it may reveal clues to alternative causes of hypercalcemia. While parathyroid adenomas are rarely palpable, a firm neck mass in the setting of hypercalcemia should raise suspicion for parathyroid carcinoma. Patients may present with a wide range of

symptoms due to hypercalcemia and its systemic effects, including abdominal pain, loss of appetite, constipation, and polyuria, as well as musculoskeletal complaints such as bone pain, fractures, osteoporosis, and muscle weakness. Neuropsychiatric manifestations like depression, memory loss, headaches, fatigue, and difficulty concentrating are also common, while cardiovascular complications can include hypertension, arrhythmias, aortic valve calcification, left ventricular hypertrophy, and increased risk of coronary artery disease [2]. Previous animal studies have reported impaired energy production, transfer, and utilization, as well as enhanced proteolysis of skeletal muscle in response to PTH. In patients with kidney failure and severe secondary hyperparathyroidism, resting energy expenditure increases compared to mild to moderate hyperparathyroidism. Elevated resting energy expenditure leads to skeletal muscle wasting through enhanced fat and protein catabolism. Parathyroidectomy has been shown to result in a decline in resting energy expenditure within six months, followed by an increase in body weight and an improvement in muscle weakness. The influence of primary and secondary hyperparathyroidism on glucose, fat, and protein catabolism has been explored since the 1980s. Patients with kidney failure and secondary hyperparathyroidism exhibited increased catabolism, characterized by higher rates of glucose and fat turnover. In contrast, patients with primary hyperparathyroidism demonstrated limited suppression of endogenous glucose turnover and higher rates of net protein loss [3]. Hypercalcemia is not an uncommon finding in malignancy, but the pathophysiology causing it varies. Calcium homeostasis is primarily regulated by a complex reciprocal interaction of hormonal signals, with parathyroid hormone (PTH) serving as an elementary modulator. Physiologically, PTH is released in response to low serum calcium by the parathyroid gland, which stimulates the production of calcitriol, also known as 1,25-dihydroxycholecalciferol or 1α,25-dihydroxyvitamin D3, by the kidneys and regulates phosphate and calcium by acting on the kidneys, bones, and GI tract [4].Clinically, hypercalcemia accompanied by elevated PTH levels perpetually indicates primary hyperparathyroidism, most often due to a solitary adenoma, and less frequently to parathyroid hyperplasia or carcinoma. The diagnostic description, therefore, is built on the primary hypothesis that elevated PTH originates from parathyroid tissue.

In the 1920s, hypercalcemia in malignancy was believed to result from bone destruction by cancer cells. By 1941, researchers discovered that certain tumors secrete a hormone resembling PTH. With advances in biomedical technology in the late 1980s, this protein was identified and named parathyroid hormone–related peptide (PTHrP) due to its similarity to PTH [5]. However, PTH stimulates the release of calcitriol, which helps to absorb calcium by the gut, the only difference between them in terms of mechanism. Some malignancies cause bone metastases that release cytokines, stimulating osteoclast activity, which in turn increases bone resorption and raises serum calcium levels [6-8].

In regard to malignancy-related hypercalcemia, the most frequent causes include humoral malignancy, where most solid tumors and lymphoma produce parathyroid hormone-related protein (PTHrP), metastatic tumor osteolysis, and tumor production of calcitriol. True ectopic production of biologically active PTH by a non-parathyroid malignancy is extremely rare, with reported cases primarily involving squamous cell carcinoma, small cell lung cancer, and ovarian cancer [6,9-11].

Here, we present a case of a patient whose presentation questioned the conventional diagnostic approach, a case of raised, symptomatic hypercalcemia with markedly elevated intact PTH levels, possibly traced to ectopic PTH production by a non-parathyroid tumor.

Case presentation

A 73-year-old female with a history of chronic kidney disease (CKD), heart failure with preserved ejection fraction, hypertension, and type 2 diabetes mellitus presented to the emergency department with progressive altered mental status. On presentation, she was febrile, hypertensive, and had tachycardia. Her urinalysis revealed leukocyte esterase positivity, 3+ bacteria, and numerous white blood cells. Urine culture grew Citrobacter species, and intravenous antibiotics were initiated. Her hepatitis panel was negative, and ammonia levels were normal, ruling out the potential hepatic encephalopathy.

Laboratory evaluation revealed an elevated calcium level of 11.5 mg/dL (normal: 8.5–10.2 mg/dL) and elevated alkaline phosphatase 160 IU/L (30-130 IU/L) (Figure 1). Hypercalcemia improved with hydration using intravenous fluids and calcitonin.

To investigate the underlying cause of hypercalcemia, parathyroid hormone (PTH) was subsequently measured and found to be elevated at 113 pg/mL (normal: 15–65 pg/mL). Additional workup included a nuclear medicine parathyroid gland scan, which was negative, excluding the primary hyperparathyroidism (Figure 2). Further investigations ruled out other common causes of hypercalcemia, including multiple myeloma, PTH-related peptide (PTHrP)-mediated hypercalcemia, secondary hyperparathyroidism from CKD, vitamin D-related disorders, and osteolytic metastases.

A contrast-enhanced computer tomography (CT) and pelvis revealed an enlarging right retroperitoneal mass measuring 4.3 cm, suspicious for malignancy (Figure 3). Biopsy demonstrated metastatic adenocarcinoma (Stage IV) of the gastrointestinal tract, with an immunoprofile suggesting a primary site in the upper GI tract, including the pancreas and biliary system.

Figure 1: Laboratory Values starting with the most recent

	Calcium	PTH	PTHrp	Calcitriol	Ionized Ca^{+2}	Vit -D	Phosphorus	ALP
08/13/2024	12.0 mg/dL	113 pg/mL	0.4 pmol/L	24 pg/mL	1.55 mmol/L	49.2ng/mL	2.9 mg/dL	160 IU/L
11/23/2023	10.9 mg/dL	50.3 pg/mL	-	-	-	45 ng/mL	-	-
09/18/2023	10.5 mg/dL	-	-	-	-	-	-	-
11/30/2021	10.5 mg/dL	-	-	-	-		-	-

Reference values: (Calcium 8.4-10.2mg/dL), (PTH 12-88 pg/ml), (PTHrp < or = 4 pmol/L), (Phosphorus 2.3-4.7mg/dL), (calcitriol 24.8 – 81.5 pg/mL), (Ionized Calcium 1.12-1.32mmol/L), (Vitamin D 25- OH 29-99ng/mL), (ALP 30-130 IU/L)

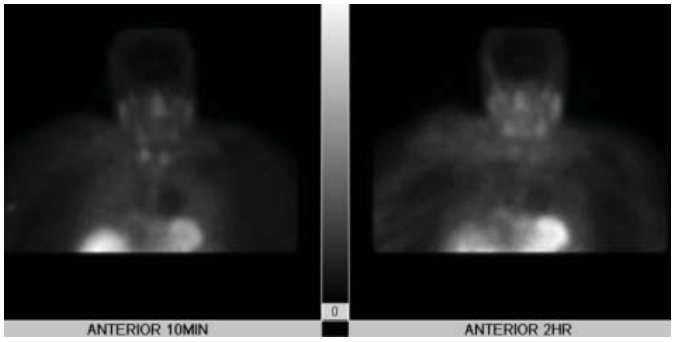

Figure 2: Nuclear Medicine Parathyroid Scan with complete washout of thyroid and parathyroid glands.

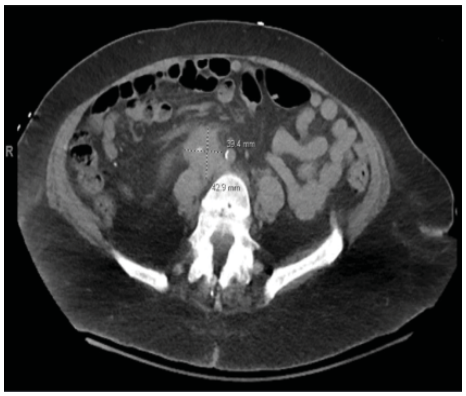

Figure 3: Contrast-enhanced CT of abdomen and pelvis showing right retroperitoneal mass.

Although malignancy is a well-known cause of hypercalcemia, in this patient, the hypercalcemia was strongly suspected to be due to ectopic parathyroid tissue, rather than tumor-mediated mechanisms. Further evaluation for ectopic PTH secretion could not be completed due to the patient's transition to hospice care.

Review of her previous records revealed a chronic history of hypercalcemia, elevated ALP, and elevated PTH. In 2023, the patient presented with weakness, dizziness, and abdominal pain. Imaging at that time revealed right hydronephrosis with a 2 mm non-obstructing ureteral stone. Further evaluation revealed hypercalcemia, accompanied by high ALP and elevated PTH levels.

This clinical scenario was initially suspected to be consistent with primary hyperparathyroidism. The negative parathyroid scan ruled out the suspicion, and no alternative diagnoses were considered at that time. Despite elevated calcium and PTH levels, no further investigations were performed at that time. Perhaps a thorough history and detailed imaging could have identified the etiology sooner.

Discussion

Hypercalcemia is a common metabolic complication in patients with malignancy, but the underlying mechanisms are heterogeneous and require careful evaluation. Most cases of cancer-related hypercalcemia are mediated either by humoral factors, such as parathyroid hormone–related peptide (PTHrP), or by local osteolytic effects of metastatic lesions. Less frequently, malignancies can produce calcitriol, contributing to elevated serum calcium levels. Ectopic secretion of biologically active PTH by non-parathyroid tumors is extremely uncommon, with only a few cases reported in the literature, including its occurrence by endometrioid carcinoma, small-cell lung carcinoma, and ovarian cancer [5]. This rare occurrence can make the diagnosis challenging, particularly when the presentation closely mimics more common causes of hypercalcemia.

In this patient, persistent hypercalcemia was accompanied by elevated intact PTH levels, a finding that is classically suggestive of primary hyperparathyroidism [12]. However, parathyroid imaging was repeatedly negative, ruling out primary parathyroid adenoma or hyperplasia. Although surgical exploration of the parathyroid glands could have further confirmed the diagnosis, imaging and serologic markers strongly suggest ectopic secretion of parathyroid hormone. Further investigations excluded PTHrP-mediated hypercalcemia, vitamin D-related disorders, secondary hyperparathyroidism from CKD, multiple myeloma, and osteolytic metastases, which are the more typical causes of hypercalcemia in patients with malignancy.

Importantly, reviewing her records also revealed a history of chronic hypercalcemia, elevated alkaline phosphatase, and elevated PTH. Despite abnormal labs, further evaluation was not performed at that time except for parathyroid imaging, which was negative.

The combination of persistent high calcium, elevated PTH, high alkaline phosphatase, and negative parathyroid scans strongly raised suspicion for ectopic PTH production, particularly when there is a presence of confirmed malignancy, an extremely uncommon cause of hypercalcemia.

Conclusion

This rare cause left her hypercalcemia unresolved

and illustrates how rare etiologies, such as ectopic PTH secretion, can be easily overlooked, leading to repeated missed opportunities for timely diagnosis despite consistent biochemical abnormalities. Timely consideration and diagnosis of this rare condition is important for the management of this etiology at an early stage, which could prevent long-term morbidity.

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We confirm that the authorship requirements have been diligently met, and the final version of the manuscript has been unanimously approved by all contributing authors.

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