

Hypercalcemia and Cancer: Differential Diagnosis and Treatment

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Abstract: Incidentally detected hypercalcemia usually presents in an indolent manner and is most likely caused by primary hyperparathyroidism. In contrast, hypercalcemia in the patient with a history of cancer presents in a wide range of clinical settings and may be severe enough to warrant hospitalization. This form of hypercalcemia is usually secondary to hypercalcemia of malignancy and can be fatal. Hypercalcemia of malignancy is most commonly mediated by tumoral production of parathyroid hormone–related protein or by cytokines activating osteoclast degradation of bone. The initial workup, differential diagnoses, confirmatory laboratory testing, imaging, and medical and surgical management of hypercalcemia are described in the patient with cancer. **CA: A Cancer Journal for Clinicians 2018;68:377-386. © 2018 American Cancer Society.**

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Case Scenario 1

A 55-year-old man presents to clinic with the chief complaint of an elevated calcium level (10.8 mg/dL, reference range 8.4–10.2 mg/dL) noted during routine laboratory testing by his primary care provider. His past medical history is significant for prostate cancer, which was treated 2 years ago with prostatectomy, and his current prostate-specific antigen level is 0.0 ng/mL. A review of records demonstrates the presence of hypercalcemia since at least 3 years prior, with calcium levels ranging from 10.2 to 10.8 mg/dL. His parathyroid hormone measurement is elevated at 127.5 pg/mL (reference range, 9–80 pg/mL). Bone mineral density demonstrates osteoporosis, with a T-score of –2.6 in the forearm. He describes an episode of nephrolithiasis 9 years prior.

Case Scenario 2

A 21-year-old woman who had a history of stage IV melanoma with metastases to lung and bones that was refractory to treatment presented to the oncology clinic with altered mental status. She was sent to the emergency room and found to have a calcium level of 15 mg/dL. Her parathyroid hormone measurement was 4.0 pg/mL.

Introduction

Calcium homeostasis is tightly regulated but can be derailed by multiple benign or malignant processes, all of which may occur in the patient with cancer. Presentations of these conditions range from asymptomatic disease incidentally detected on screening laboratory tests to severe metabolic derangements. This article reviews the causes of hypercalcemia in the patient with cancer and describes the diagnostic steps and treatment options for the most common causes of hypercalcemia.

Many organs are involved in the regulation of calcium. Chief among these are the parathyroid glands and, when calcium levels drop, the parathyroid glands increase secretion of parathyroid hormone (PTH). PTH binds to the PTH receptor and causes several downstream effects, which cause serum calcium levels to increase. PTH causes osteoblast induction of osteoclasts' resorption of calcium from

the bone. It also causes the kidney to increase calcium reabsorption and convert vitamin D to its active form, as discussed below. All of these mechanisms serve to increase serum calcium levels.¹

Vitamin D, which is partially regulated through PTH, also plays an important role in the regulation of calcium. The first step of vitamin D metabolism occurs at the skin, where ultraviolet light catalyzes the production of Vitamin D₃, also called cholecalciferol, from 7-dehydrocholesterol. Cholecalciferol is then hydroxylated at the 25 position by the liver to form 25-hydroxycholecalciferol, also called calcifediol. Calcifediol is then hydroxylated at the 1 position in the kidney to form 1,25-dihydroxycholecalciferol, or calcitriol. This final step is regulated by PTH, and calcitriol is the active form of vitamin D. Calcitriol increases serum calcium by causing increased calcium absorption in the intestines, increased calcium reabsorption in the kidneys, and stimulation of osteoblasts to reabsorb calcium from bone.^{1,2}

The parafollicular C cells of the thyroid gland secrete calcitonin. Calcitonin decreases calcium levels by inhibiting osteoclast activity and renal reabsorption of calcium. In the adult, this has a small to negligible effect on calcium homeostasis.¹

In the healthy adult, the net daily calcium balance is zero. The majority of calcium is stored in the bone. The bone stores approximately 1000 g of calcium, and about 280 mg of this is turned over each day. Another 1000 mg is in circulation in the extracellular fluid. The average adult consumes approximately 1000 mg of calcium in their diet, of which 500 mg is absorbed, and the intestines secrete 325 mg, leading to a net absorption of 175 mg daily, and the rest is excreted in the feces. The kidney excretes about 175 mg of calcium a day in the urine, leading to a net balance of zero.¹

Calcium exists in the serum as both free ionized calcium and bound calcium. Most of the bound calcium is attached to albumin, and the rest is bound to other proteins or small anions. Tests for total serum calcium measure both forms of calcium. This level can vary based on the level of calcium-binding proteins. If a patient has hypoalbuminemia, the total serum calcium will be artificially low, and a corrected calcium level should be calculated. Another option is to measure the ionized calcium level directly, which will be a better indicator of bioavailable calcium in the serum. The ionized calcium level is also regulated by the pH of the serum. Calcium binding to extracellular proteins is increased with increasing pH.

Hypercalcemia has many clinical manifestations, which are mostly independent of etiology and affect multiple organ systems. In the kidney, hypercalcemia can lead to nephrolithiasis, which may be silent or symptomatic. Chronic

renal insufficiency may occur. Polyuria is also common and, combined with decreased oral intake, can lead to hypovolemia. Gastrointestinal manifestations include nausea, vomiting, and constipation and may be attributable to calcium's influence on smooth muscle. Pancreatitis may also occur, although the mechanism for this is unknown. Calcium also induces increased gastrin secretion, so that hypercalcemia may lead to peptic ulcers. The effects of hypercalcemia on the central nervous system include anxiety, depression, and cognitive dysfunction, and patients who have markedly elevated serum calcium levels may present with lethargy, confusion, stupor, or even coma. Mild neurocognitive dysfunction occurs more frequently in hyperparathyroidism than in hypercalcemia from other causes and may be caused by the direct effect of PTH on the brain.³ Finally, when hypercalcemia is the result of a resorptive process, patients may also present with fragility fractures caused by osteopenia and osteoporosis.¹

Patients with cancer who have hypercalcemia can be divided into 2 major groups: those with and those without an elevated PTH level. The most common cause of inappropriately elevated PTH in all patients is primary hyperparathyroidism (PHPT). In developed countries, it usually presents incidentally with an indolent course and is most often discovered from a screening serum calcium level obtained for other reasons.^{4,5} Interestingly, with the advent of the electrolyte panel, which automatically includes a serum calcium level, the incidence of PHPT has increased. Parathyroid cancer is also a possibility in patients who present with an extremely elevated PTH level—although it is rare. Other forms of malignancy may also disrupt calcium homeostasis, and, in this situation, PTH levels typically are low. Hypercalcemia of malignancy (HCM) typically is associated with severe clinical signs and symptoms and is often an oncologic emergency.⁶ Ninety percent of all cases of hypercalcemia in patients with and without cancer are caused by either HCM or PHPT. In ambulatory patients, a higher proportion will have PHPT and, in hospitalized patients, a higher proportion will have HCM.^{7,8} Figure 1 is a general algorithm that can be used when evaluating and treating a patient with hypercalcemia and a history of cancer.

Initial Evaluation of the Patient With Hypercalcemia

The initial evaluation of a patient with hypercalcemia should include a thorough history and physical. A focus should be placed on the above-mentioned signs, symptoms, and associated diagnoses of hypercalcemia. Incidental hypercalcemia may be the first manifestation of an undiagnosed malignancy. The patient should be asked about the

presence of cough, weight loss, or new masses and should be up to date with current guidelines regarding screening for colorectal, breast, and other cancers appropriate for the patient's age, sex, and risk factors. Past medical history should include information about cardiac and renal function and previous or current malignancies. A history of smoking and exposure to other carcinogens, such as alcohol abuse and sunburns at an early age, also should be elicited as well as the use of medications that may alter calcium homeostasis (commonly, thiazide diuretics or lithium).⁹

In addition to a thorough physical examination evaluating for masses (head and neck, oropharynx, breast, abdomen, rectal), physical manifestations of hypovolemia, such as tachycardia, mucosal dryness, and skin tenting, should be noticed. As discussed above, these patients can become markedly hypovolemic. Attention should be paid to family history of hyperparathyroidism, renal stones, or cancer. Occasionally, hypercalcemia is the presenting sign of cancer, and a retrospective study found that patients with hypercalcemia had a higher incidence of cancer at 1 year than those without hypercalcemia.¹⁰

After a thorough physical examination, the next step is to obtain laboratory values for levels of serum calcium, intact PTH, creatinine (to assess renal function), and a 24-hour urine collection for calcium and creatinine.⁹ The 24-hour urine can help rule out other causes of

hypercalcemia, such as familial hypocalciuric hypercalcemia (FHH), as discussed below. An ionized calcium level, an albumin level, and a pH level can be obtained when there is a suspicion of spurious calcium elevations.

The PTH level will act as a fork in the diagnostic road: in a patient with high PTH, the most likely diagnosis is primary hyperparathyroidism, and the next step will be to determine whether the patient has indications for surgical treatment (see below). In a patient with low PTH, the most likely diagnosis is HCM, and evaluation for an underlying malignancy should be pursued.^{6,8} Patients with low PTH should have their PTH-related protein (PTHrP) level checked to evaluate for humoral HCM (HHM). PTHrP is a protein produced by some cancers and, in some tissues, has effects similar to those of PTH. It is discussed further below. If the PTHrP is normal, then levels of 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D can be assessed to help diagnose other forms of HCM.

Patients With Inappropriately Elevated PTH

Primary Hyperparathyroidism

Unsuppressed or inappropriately elevated PTH refers to a high PTH level in the setting of a high or high-normal calcium level. Patient with low calcium may have an appropriate increase in their serum PTH as a compensatory mechanism.

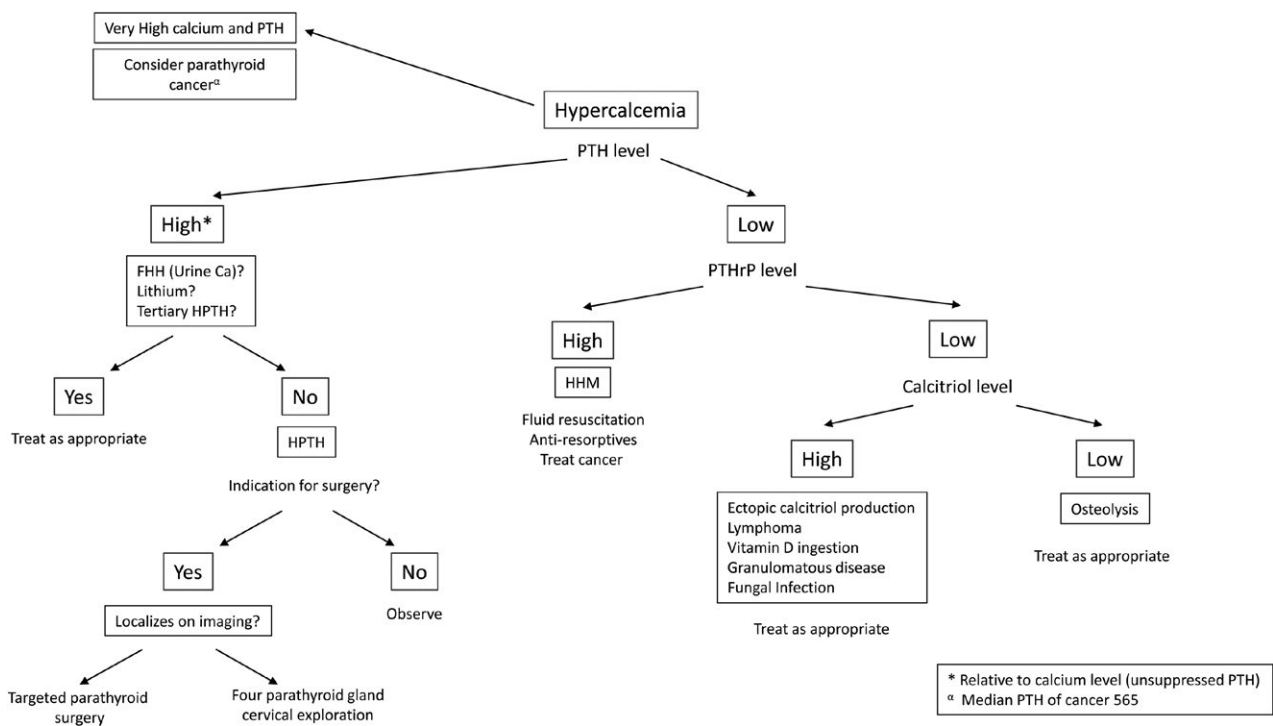


FIGURE 1. Algorithm for the Evaluation and Treatment of a Patient With Hypercalcemia and a History of Cancer. FHH, familial hypocalciuric hypercalcemia; HHM, humoral hypercalcemia of malignancy; HPTH, hyperparathyroidism; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; Urine Ca, urine calcium.

Although there is no standard, any PTH greater than 20 pg/mL is often considered unsuppressed. Hypercalcemic patients with an unsuppressed PTH level may have PHPT from a single parathyroid adenoma, multigland disease (more than 1 parathyroid adenoma), 4-gland parathyroid hyperplasia associated with multiple endocrine neoplasia type 1, secondary hyperparathyroidism from chronic kidney disease, chronic lithium use, parathyroid carcinoma, or (rarely) familial hypercalciuric hypercalcemia.⁹ Of these, PHPT associated with a single adenoma is the most common cause of hypercalcemia in the general population and also can be seen in the cancer population, although it is less common. PHPT is responsible for 6% to 21% of hypercalcemia among patients with cancer,^{11,12} so it is important to remember that not all cases of hypercalcemia in patients with cancer are because of their malignancy. One retrospective study indicated that noncancer causes of hypercalcemia accounted for 97% of patients in remission and 21% of those who had active cancer, with PHPT causing 75% of those cases. Other benign causes included sarcoidosis, milk alkali syndrome, and undiagnosed causes.¹³ Therefore, the PTH level must always be checked in a patient with cancer who presents with hypercalcemia.

The most predominant presentation of PHPT in the United States, Canada, and Europe is that of the seemingly asymptomatic patient who has incidentally identified hypercalcemia noted on routine laboratory testing.^{4,5} Clinical manifestations of PHPT that initially may be attributed to other causes include nephrolithiasis, osteopenia/osteoporosis with or without pathologic fractures, neurocognitive decline, gastrointestinal symptoms, musculoskeletal pain, and potentially increased cardiovascular mortality.^{9,14,15} In areas with poor access to health care, patients may present with

brown tumors of bone, which are the product of long-standing osteoclast overactivity (Fig. 2A).

Treatment of Primary Hyperparathyroidism

After a diagnosis of PHPT is made, parathyroidectomy should be considered for all symptomatic patients and most asymptomatic patients. Nephrolithiasis, fragility fractures (also known as pathologic fractures), osteoporosis, or evidence of spinal compression fractures are manifestations of symptomatic PHPT. In patients without objective evidence of disease, parathyroidectomy is indicated in the following situations: a serum (albumin-corrected) calcium level greater than 1 mg/dL above normal, bone health risk (a dual-energy x-ray absorptiometry scan less than -2.5 , indicating osteoporosis or vertebral fracture on imaging), patients younger than age 50 years (who require prolonged monitoring and have a higher incidence of progressive signs and symptoms), or evidence of silent renal involvement (asymptomatic nephrolithiasis on imaging, nephrocalcinosis, hypercalciuria [defined as a 24-hour urine calcium level greater than 400 mg/dL], or impaired renal function [defined as a glomerular filtration rate less than 60 mL/minute]).⁹ Other findings that should prompt consideration for parathyroidectomy in patients without frank, objective evidence of disease were previously debated, because there is less definitive evidence that they are caused by the PHPT, and they are often multifactorial in nature. These include frailty or diminished functional capacity, gastroesophageal reflux, neurocognitive dysfunction, and (less commonly) fibromyalgia or cardiovascular disease.^{9,16,17} In patients with normocalcemic hyperparathyroidism, it is important to rule out secondary hyperparathyroidism—most commonly from vitamin D deficiency.

Once the diagnosis is rendered, it must be determined whether the patient is a surgical candidate for parathyroidectomy. This should be a decision that includes the patient and a surgeon. The next step in management is to determine whether the disease is because of a single adenoma or multiple-gland disease. Imaging modalities, including ultrasound, 4-dimensional computed tomography, and sestamibi scanning, can help localize the overactive gland; the exact modality chosen depends on the expertise and availability of the region. If the disease is localized to a single adenoma on imaging, then a focused resection is planned. In this approach, the suspected gland is resected without exploring the other 3 glands. Adequacy of resection of all hyperfunctional tissue is confirmed by using an intraoperative PTH measurement. If the PTH level does not drop after resection of a single suspected adenoma, then all 4 glands are examined intraoperatively. This is termed *bilateral cervical exploration* and was historically the

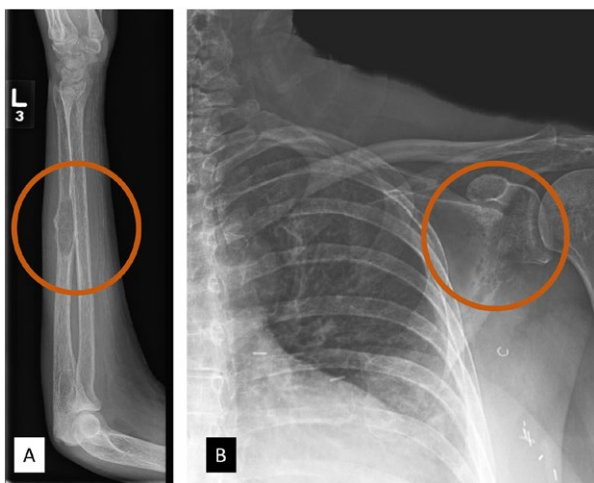


FIGURE 2. (A) Brown Tumor Associated With Long-Standing Hyperparathyroidism. (B) Osteolytic Bone Lesion From Metastatic Breast Cancer. Courtesy of Dr. Steven Waguespack.

standard operative approach for patients with PHPT. It is also recommended for patients who have a family history of disease or are at risk for multigland disease, and it remains as a viable approach for all patients with PHPT.¹⁸

Observation and/or pharmacologic management of PHPT is not therapeutically or cost-effective for patients who are surgical candidates, regardless of symptomatology.⁹ For the patient who cannot undergo surgery, medical options tailored to the individual patient include antiresorptives for osteoporosis (bisphosphonates or denosumab) or the calcium-sensing receptor agonist cinacalcet for hypercalcemia control.¹⁹

Other Causes of an Elevated PTH

The differential diagnosis for an elevated PTH level in the setting of hypercalcemia includes tertiary hyperparathyroidism, hypercalcemia due to medications (eg, lithium therapy), FHH, parathyroid cancer, or (rarely) PTH-producing cancers.⁹

Secondary hyperparathyroidism is associated with chronic kidney disease or vitamin D deficiency. Chronic kidney disease leads to reduced calcitriol levels, elevated phosphate, and low calcium. These factors increase PTH production and parathyroid cell proliferation. Tertiary hyperparathyroidism occurs when the parathyroid glands become autonomously functional after correcting the inciting cause of secondary hyperparathyroidism and mediating hypercalcemia. It is thought to be caused by induced and irreversible hyperplasia. Treatment of tertiary HPT in the setting of renal disease is beyond the scope of this review but may include surgery for selected patients. This is typically a subtotal parathyroidectomy in which 3.5 glands are removed. There are reserved indications for patients who have failed this treatment or in other select circumstances to perform a total parathyroidectomy with autotransplantation—but this is not the preferred initial operation.

Hypercalcemia caused by either thiazide diuretics or lithium resolves with cessation of the medication; however, this may be particularly difficult in cases of bipolar disease managed with lithium when there are limited treatment alternatives.²⁰ The mechanism of lithium's effect on parathyroid function is not well delineated but is thought to be related to the calcium-sensing mechanism of the glands.²¹ Well-selected patients with lithium-induced hypercalcemia may benefit from subtotal parathyroidectomy and often demonstrate multigland disease.²²

Familial hypocalciuric hypercalcemia is characterized by low urinary calcium excretion (defined as a calcium-to-creatinine clearance ratio less than 0.01 and 24-hour urinary calcium excretion less than 100 mg) in the setting of hypercalcemia.^{5,9} In FHH, an autosomal-dominant inherited

mutation in the calcium-sensing receptor (CaSR) gene results in the inability of the parathyroid glands and kidneys to recognize alterations in serum calcium levels. Higher calcium levels are needed to lower PTH secretion, and the kidneys reabsorb more calcium. Although occasionally patients with FHH manifest symptoms of hypercalcemia and thus should be monitored clinically, they do not benefit from parathyroidectomy.

Up to 42% of adults have vitamin D deficiency,⁵ which results in compensatory, mild PTH elevation. Calcium and phosphorus levels can be normal or at the low end of normal ranges. A trial of vitamin D supplementation is both diagnostic and therapeutic and does not have any adverse effects in the setting of concomitant PHPT.²³

Hereditary hyperparathyroidism (ie, multiple endocrine neoplasia type 1 and, less likely, multiple endocrine neoplasia type 2A, as well as others)⁹ should be considered in patients younger than 40 years who present with hypercalcemia, patients with multigland disease, or those with a strong family history or syndromic manifestations. These patients should undergo genetic counseling.

Parathyroid carcinoma (PC) may be suspected preoperatively in the setting of marked hypercalcemia (greater than 14 mg/dL), PTH more than 3 or 4 times normal levels, or based on intraoperative findings such as local invasion. One study indicated that the median PTH for PC was 565 pg/mL.²⁴ Typical parathyroid adenomas are soft and easily separated from the surrounding tissues, but PC is typically hard and adherent to surrounding tissues, being difficult to remove. Surgeon judgement is a critical part of the diagnosis. PC is rare (less than 1% of all cases of PHPT) and often is not diagnosed until after surgery.²⁵ Once the diagnosis of PC is established, these patients should be referred to a tertiary facility with multidisciplinary teams specialized in the treatment of PC.^{24,26,27} Surgical treatment goals are to resect all tumor with negative margins without fracture of the specimen and without causing spillage of tumor cells onto the surgical field; resection of adjacent, uninvolved compartments is not necessary. When the disease is not resectable, the calcimimetic cinacalcet can be used to partially suppress PTH secretion by the tumor.²⁸

Patients With Low PTH

Patients with low PTH and high calcium most likely have HCM. Common causes of HCM include HHM and local bone osteolysis. Less common causes include excess calcitriol (1,25-dihydroxyvitamin D) production by lymphomas.⁶ HCM occurs in 20% to 30% of patients who have advanced cancer, with a yearly incidence of 1% to 2% across all cancer types.^{6,29,36,37} It is the most common cause of hypercalcemia in the hospitalized patient.^{7,38}

It is a poor prognostic sign, and patients with HCM have a mean survival of 2 to 3 months and an in-hospital mortality of 6.8%.^{19,39} With the exception of neuroendocrine tumors, most tumors are clinically evident when they cause HCM.⁶ Although any cancer can lead to HCM, the most common associated malignancies are solid cancers, such as lung, breast, head and neck, and urinary tract cancers. Multiple myeloma is also commonly a cause of HCM.^{33,38}

Presenting signs and symptoms of HCM include nausea, vomiting, anorexia, abdominal pain, constipation, polydipsia, polyuria, hypotension, bone pain, fatigue, and confusion. The severity of symptoms is related to the level of hypercalcemia as well as the rate of rise of the calcium. The presentation is rarely asymptomatic, and patients commonly present with markedly elevated serum calcium levels (>14 mg/dL).⁶ These patients are markedly dehydrated because of decreased oral intake, vomiting, and nephrogenic diabetes insipidus. Advanced cases can lead to renal failure, cardiac failure, coma, and death.

Historically, experts recommended against routine testing of PTHrP in the workup of HCM, because laboratory assays were unreliable, slow, and costly, and HHM was the most likely diagnosis regardless.⁶ The accuracy and reliability of laboratory assays for PTHrP have since improved because of newer double-antibody techniques, and now a PTHrP level should be checked in all patients with suspected HCM. Furthermore, when elevated at presentation, PTHrP can be used as a biomarker to assess treatment response to therapy.⁴⁰⁻⁴²

Humoral Hypercalcemia of Malignancy

Systemic secretion of PTHrP by malignant tumors is referred to as HHM. It is responsible for 80% of cases of HCM.^{6,38} The most common tumors associated with this syndrome are squamous cell carcinomas of the lung, head and neck, esophagus, skin, or cervix or carcinomas of the breast, kidney, prostate, or bladder.¹³

Although PTHrP serves a physiologic role in embryologic development and in mammary gland function, it has no other known functional role in adult metabolism.⁴³ It shares close homology to PTH at its N-terminus and activates the type 1 PTH receptor, but it is encoded by a different gene.⁴⁴ Both PTHrP and PTH increase calcium reabsorption in the kidney and stimulate osteoblasts to secrete receptor activator of nuclear factor- κ B ligand (RANKL), which binds to the RANK receptor on osteoclasts.^{45,46} This interaction mediates the differentiation of osteoclast precursors into mature osteoclasts and increases bone resorption by osteoclasts.

Bone Osteolysis

Osteolysis mediated by local tumor cell secretion of osteoclast-activating cytokines accounts for 20% of the cases of HCM and is most commonly seen in patients with breast cancer and multiple myeloma (Figure 2B).^{6,29,47} Activating cytokines include macrophage inflammatory protein 1 α , interleukin 1 (IL-1), IL-3, IL-6, tumor necrosis factor α (TNF- α), TNF- β , lymphotoxin, and prostaglandins.⁴⁸ The osteolysis is not caused by direct tumor invasion and degradation of bone—a common misconception. Instead, cytokines released by the tumor and surrounding cells, such as macrophages and endothelial cells, act similarly to PTH and PTHrP to cause increased secretion of RANKL by osteoblasts, which stimulates osteoclast differentiation and increased resorption of bone. Osteoblast function is also inhibited. Furthermore, the production of osteoprotegerin, an inhibitor of RANKL, is decreased. All of these lead to increased bone resorption.^{49,50} Clinically, HHM and bone osteolysis differ from each other by PTHrP level, with elevated levels in HHM and low levels in bone osteolysis.

Other Causes of Hypercalcemia and Hypercalcemia With Low PTH

HCM can also be caused by excessive production of calcitriol, the active form of vitamin D. This is an uncommon entity and is responsible for less than 1% of HCM cases overall.⁶ It is typically associated with lymphomas but has also been reported in other malignancies. From 5% to 15% of patients with Hodgkin lymphoma will develop hypercalcemia, and this is almost always secondary to tumor-mediated overproduction of calcitriol.^{55,56} The tumor cells or surrounding lymphocytes overexpress 1 α -hydroxylase, which causes ectopic conversion of 25 hydroxyvitamin D to 1,25-dihydroxyvitamin D.^{57,58} The hypercalcemia of excess calcitriol production is because of both increased intestinal and bone reabsorption of calcium. Unlike other forms of HCM, calcitriol-mediated HCM tends to be associated with a normal to high phosphorus level.²⁹

Another rare cause of HCM is pseudohypercalcemia caused by increased secretion of calcium-binding immunoglobulins that occurs in patients with multiple myeloma. The immunoglobulins increase total serum calcium by binding inactive calcium. The bioavailable calcium is unchanged and, in these patients, an ionized calcium level should be obtained.⁵⁹ These patients typically are asymptomatic and have mild elevations in total calcium.

Nonmalignant causes of hypercalcemia causing a suppressed PTH include over-ingestion of antacids

containing calcium (milk-alkali syndrome), thiazide diuretic use, or over-replacement with vitamin A or D. Hypercalcemia secondary to vitamin A toxicity is a rare and poorly understood phenomenon.⁶⁰ Granulomatous diseases, such as sarcoidosis, or fungal infections can cause hypercalcemia through the ectopic production of calcitriol by activated mononuclear cells in the lungs and lymph nodes. Finally, hyperthyroidism, adrenal insufficiency, pheochromocytoma, and chronic immobility also can cause hypercalcemia through increased osteoclast activity.¹³

Treatment of HCM

Once the diagnosis is made, the first step in the management of a patient in hypercalcemic crisis is to stabilize the patient with intravenous fluid resuscitation. After correction to euvolemia with normal saline, there are multiple medications that can be used to reduce the serum calcium level, including bisphosphonates, corticosteroids, calcitonin, and denosumab (a RANKL inhibitor). Ultimately, the inciting cause—the cancer—must be treated, or the situation will not improve. There should be strong consideration for the involvement of a palliative care specialist, because HCM is a poor prognostic indicator, and correction of the HCM does not improve survival.^{39,47}

Patients presenting with HCM are usually markedly hypovolemic and often have manifestations of renal and cardiac failure. This is because of polyuria secondary to calciuresis and also to decreased oral intake secondary to nausea and vomiting. As the patient's dehydration worsens, this worsens the renal and cardiac failure. Reversing the hypovolemia will also increase the glomerular filtration rate and aid in the excretion of calcium. The first step in treatment, therefore, is fluid resuscitation. This is usually done with normal saline to a goal urine output greater than 75 cm³/hour. Patients often require 1 or 2 liters as an initial bolus and then a maintenance rate of 150 to 300 cm³/hour to maintain adequate urine output. Care must be taken to avoid volume overload, especially in patients with acute or chronic renal and cardiac insufficiency.

Other supportive measures include correcting hypophosphatemia, because this may worsen the hypercalcemia. All oral calcium intake should be stopped.^{6,61} Oral phosphate should be used when feasible, because intravenous phosphate has been associated with severe hypocalcemia, seizures, and acute renal failure.^{62,63}

Loop diuretics were historically recommended in the treatment of HCM once the patient was euvolemic, because they increase urinary calcium excretion. However, this practice has fallen out of favor because it has not been shown to be beneficial and can lead to electrolyte abnormalities.^{64,65}

Diuretics can be used to treat patients who become fluid-overloaded after aggressive resuscitation. Thiazide diuretics should not be used, because they increase calcium reabsorption.⁶⁴

The next step in management usually includes intravenous administration of bisphosphonates; oral bisphosphonates are not efficacious in the setting of HCM. Oral bisphosphonates do not lead to serum concentrations that are high enough to deactivate osteoclasts, and they are only approved for the treatment of osteoporosis. Modern-generation intravenous bisphosphonates include pamidronate (60-90 mg intravenously over 2-6 hours) and zoledronic acid (4 mg intravenously over 15-30 minutes). They are the most studied and are considered the most effective agents for treatment of the HCM.⁶⁶ They work by inhibiting the osteoclasts from degrading bone through several mechanisms. They inhibit osteoclast attachment to actin-binding sites, promote apoptosis and decrease the recruitment and development of osteoclasts, and increase expression of a decoy receptor for RANKL.⁶⁷⁻⁷⁰ Multiple studies have demonstrated the superiority of bisphosphonates and saline therapy versus saline therapy alone.^{71,72} Onset of action is slow, taking between 1 and 3 days to show effect. The calcium nadir is reached in 4 to 7 days. Response to therapy can last for 1 to 3 weeks.⁷³

Zoledronic acid is easier to administer and has been shown to have a more efficacious response than pamidronate, with a higher proportion of patients achieving normalization within 7 to 10 days of treatment and a longer duration of effect.⁷⁴ Bisphosphonates have been associated with nephrotoxicity, and care must be used, because patients with HCM usually have some degree of renal impairment.⁶⁶ It is sometimes necessary to delay administration of these medications until after the patient has been rehydrated or to reduce the dose based on the estimated glomerular filtration rate. It is safe to use these medications in patients with end-stage renal disease.^{75,76} Interestingly, although zoledronic acid has been associated with acute tubal necrosis and severe acute toxicity, pamidronate is only associated with focal segmental glomerular sclerosis leading to nephrotic syndrome, which develops over months of treatment. Therefore, pamidronate may be safe in patients with impaired kidney function, although adjustment of the dose may be required. Patients who are receiving treatment with bisphosphonates may experience bone pain or a flu-like malaise for the first day or 2 of administration.^{29,66} Other complications include nephrotic syndrome, esophageal inflammation, and osteonecrosis of the jaw with prolonged therapy.^{29,76} Osteonecrosis of the jaw is rare and typically occurs after several months of treatment.^{77,78}

Approved by the US Food and Drug Administration for the treatment of HCM in 2014, denosumab is a human monoclonal antibody that binds RANKL and prevents its binding to RANK on osteoclasts, decreasing osteoclast resorption of bone.⁷⁹ It is administered subcutaneously (120 mg every 4 weeks, with loading doses on days 8 and 15), and the response time is 9 days, with an extended response of up to 104 days.^{80–82} It has been shown to be useful in bisphosphonate-refractory HCM, and a phase 3 study demonstrated that denosumab was superior to zoledronic acid for the prevention of HCM in patients with metastatic bone disease.⁸³ Denosumab can lead to hypocalcemia; thus, calcium levels must be routinely checked while patients are receiving therapy, especially in those with vitamin D deficiency, renal insufficiency, and hypoparathyroidism.⁸⁴ Similarly, severe cases of hypophosphatemia can also occur. Denosumab is a promising new drug and may become first-line therapy for the treatment of HCM, but further studies are needed before it can replace current therapies. Like bisphosphonates, osteonecrosis of the jaw also may occur with the use of denosumab.⁶⁶ Other side effects include bone pain, nausea, diarrhea, and shortness of breath. Although it is not renally cleared, the effect of denosumab is more pronounced in patients with renal failure, and dose adjustment may be necessary to avoid hypocalcemia.⁴⁷

Other treatments for HCM include calcitonin, corticosteroids, and dialysis. Calcitonin (4–8 U/kg intramuscularly or subcutaneously every 12 hours) has a rapid onset of action, but its effects are mild and often transient. Furthermore, patients develop tachyphylaxis to it within 48 hours.^{85,86} Calcitonin can be useful as an initial adjunct to hydration while waiting for other treatment modalities to take effect.^{47,66} Corticosteroids are useful in the treatment of HCM because of excess calcitriol production by lymphomas. They function by inhibiting the 1α -hydroxylase that catalyzes the conversion of 25 hydroxyvitamin D to calcitriol. They also can be used to improve the efficacy of calcitonin by upregulating calcitonin receptors on osteoclasts.⁸⁷ Occasionally, patients with HCM are unable to tolerate high-volume fluid therapy because of renal or cardiac failure; hemodialysis with a low calcium bath can be considered.

Ultimately, the above measure can only temporize the problem of HCM. The underlying malignancy must be treated. The prognosis of patients with HCM is poor, and palliative specialist involvement should be strongly considered. In patients with incurable disease, if greater than 90% of

the tumor can be removed, then palliative debulking surgery may control symptoms and improve quality of life.⁸⁸ Other palliative or therapeutic options that may be used as adjuncts to debulk tumor burden include radiofrequency ablation, cryoablation, hepatic embolization, and external-beam radiation. Systemic chemotherapy can be considered for tumor regression and has been found to be useful for lung cancer.³³

Wrap-Up of Cases

Case Scenario 1

A sestamibi scan and ultrasound localized a right inferior parathyroid adenoma. A minimally invasive parathyroidectomy was performed starting with the right inferior gland, and the intraoperative PTH dropped after removal of this gland. The surgeon clinically diagnosed an adenoma, and this was confirmed on histology. The patient's calcium level returned to normal. This patient's course exemplifies one of the most common causes of hypercalcemia in the patient with cancer and the most common cause of hypercalcemia in the general population: primary hyperparathyroidism.

Case Scenario 2

The patient was admitted to the hospital and treated with intravenous fluid resuscitation and calcitonin, and her mental status improved. After sufficient intravenous hydration, she started on zoledronic acid, which lowered her serum calcium back to the normal range. She was discharged on hospital day 10, at which point she was started on denosumab because of refractory hypercalcemia. Her PTHrP level was 15 pmol/L (reference range, less than 2.0 pmol/L). This patient's course exemplifies the emergent presentation of hypercalcemia in malignancy, which, in this particular case, was caused by humoral hypercalcemia mediated by tumor production of PTHrP.

Summary

Hypercalcemia in the patient with cancer can be due to benign causes or to HCM. Serum PTH measurement is crucial in making the diagnosis. The most common benign cause is PHPT. It presents indolently and is treated with surgery when necessary. HCM usually presents with severe clinical symptoms. Treatment is focused on fluid resuscitation and correction of the calcium level. ■

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