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Hypercalcemia of Malignancy in Hospitalized Patients

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A 67-year-old white man who was a resident of a nursing home was brought to the emergency department for evaluation of sudden onset of mental status changes. His caretaker noticed that he was confused and lethargic but reported no seizure activity. The patient's other medical problems included a 75-pack-year smoking history, chronic obstructive pulmonary disease, and congestive heart failure; he experienced a myocardial infarction 1 year ago. He had no personal or significant family history of malignancy. On examination, he was found to have dry oral mucosa with loss of skin turgor. He was afebrile, blood pressure was 184/88 mm Hg, and heart rate was 126 bpm. He had a Glasgow coma score of 10 (eye: 3, verbal: 3, motor: 4) with no focal neurologic finding. His complete blood count was normal, but a metabolic profile revealed a serum calcium level of 14.2 mg/dL (ionized calcium, 1.89 mmol/L), a potassium level of 2.9 mEq/L, and a phosphorous level of 2.4 mg/dL. Electrocardiography showed only nonspecific T-wave changes. Noncontrast computed tomography (CT) of the head revealed a new left frontoparietal mass arising from the skull, causing bone destruction. Chest CT revealed a 2-cm spiculated right lung nodule, extensive mediastinal adenopathy, osseous metastatic disease, and vertebral collapse. Six to eight hours after admission, the patient developed cardiorespiratory arrest and died before further evaluation was carried out.

The major causes of hypercalcemia are primary hyperparathyroidism (PHPT) and malignancy. More than 90% of cases of true hypercalcemia that occur in ambulatory patients are caused by PHPT. Among hospitalized patients, however, only approximately 25% of cases are caused by hyperparathyroidism, with most of the remaining cases caused by malignancy (65%) or milk-alkali syndrome.[1]

Overall, hypercalcemia of malignancy (HCM) occurs in 10% to 20% of all patients with malignancy.[2] As a paraneoplastic syndrome, HCM is commonly seen in association with multiple myeloma (MM) and breast, lung, renal, and ovarian neoplasms. Hypercalcemia complicates 20% to 40% of cases of MM.[3] HCM often presents with abrupt onset, has a severe course, and generally has a poor prognosis. There are 3 major mechanisms for HCM, and a thorough understanding of these is central to a successful treatment strategy. Although most cancers may be associated with extensive bone destruction causing bone pain and hypercalcemia, in the majority of HCM cases there is no evidence of bone involvement. In 1 study, 56% of patients with HCM showed no evidence of bone metastases.[4] This article reviews the pathophysiologic mechanisms involved in HCM as well as the approach to diagnosis and treatment of this condition.

PATHOPHYSIOLOGY

The major mechanisms involved in HCM are (1) secretion of parathyroid hormone–related protein (PTHrP), which is the main mechanism for most cases of the condition known as humoral HCM; (2) direct osteolytic metastases with release of local cytokines; and (3) secretion of 1,25-dihydroxyvitamin D (1,25$[OH]_2$D; calcitriol) (**Table 1**). Hypercalcemia in cancer patients was initially thought to be due to ectopic parathyroid hormone (PTH) production. Although patients with HCM may manifest biochemical features compatible with PTH hyperstimulation (increased bone resorption, increased distal tubular calcium reabsorption, elevated excretion of nephrogenous cyclic adenosine

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TAKE HOME POINTS

- Hypercalcemia is the most common life-threatening metabolic emergency in patients with cancer.
- Hypercalcemia portends a poor prognosis and implications of therapy must be thoroughly discussed; not treating is always an option.
- Bone metastases need not be present for hypercalcemia of malignancy (HCM) to develop.
- Vigorous but careful hydration and intravenous bisphosphonates (preferably zoledronic acid) are the cornerstone of therapy.
- Calcitonin may be used as bridge therapy, and glucocorticoids are useful in steroid-responsive malignancies. Use of furosemide should be limited to volume-overloaded (often intensive care unit) patients.
- Bisphosphonates can be used in prevention of HCM in cancer patients with documented bone metastases.

Table 1. Mechanisms of Hypercalcemia of Malignancy

Mechanism	Malignancies	Frequency (%)*
PTHrP production	Squamous cell carcinomas: lung, cervical, esophageal, oral and laryngeal cancers Certain lymphomas: non-Hodgkin's, T-cell lymphoma Adenocarcinomas: breast and ovary Renal cell carcinoma Transitional cell carcinoma Multiple myeloma (rare)	88
Local osteolysis	Multiple myeloma (frequent) Solid malignancies: breast, prostate, and lung cancers Lymphomas	12
Secretion of 1,25-dihydroxyvitamin D (calcitriol)	Multiple myeloma Lymphomas: Hodgkin's, non-Hodgkin's	

PTHrP = parathyroid hormone–related protein.

*These percentages are based on Ratcliffe et al.[5] In this study, patients were divided into only "PTHrP elevated" and "non–PTHrP elevated" groups. Clearly the role of bone resorbing factors and the multiplicity of mechanisms of hypercalcemia as seen in multiple myeloma will have confounding effects on these results.

monophosphate [cAMP], hypophosphatemia, and phosphaturia),[6] studies have failed to demonstrate native PTH secretion in patients with cancer, except for those with parathyroid cancer.[7,8]

Secretion of PTHrP by malignant tumors is the main cause of hypercalcemia in patients with nonmetastatic solid malignancies (especially squamous cell lung cancer and cancers of the cervix and upper aerodigestive tract) and some non-Hodgkin's lymphomas but not in hematologic cancers such as MM.[9,10] PTHrP is a hormone elaborated by cancer cells that has (13-amino acid) N-terminal sequence homology with intact PTH, which enables PTHrP to bind with PTH receptors, stimulate cAMP production, and mimic the effects of PTH. Although PTHrP is normally present in a wide variety of tissues (eg, keratinocytes, breast, uterus, brain, parathyroid kidneys) where it performs important physiologic functions, without malignancy its level in circulation is very low. Ectopic production of PTH by tumors has been described, but this is very rare and contributes little to HCM.[11,12]

When tumor cells metastasize to bones, direct local osteolysis in areas surrounding the tumor cells can occur, resulting in bone destruction and hypercalcemia.[2] Local osteolysis contributes to hypercalcemia seen in metastatic MM and breast, prostate and non-small cell lung cancers (especially squamous cell types). However, except for MM, the main mechanism of hypercalcemia in these diseases is PTHrP production. Tumor cells metastatic to the bone appear to stimulate the production of a number of soluble osteoclast activating factors, which are potent inducers of bone resorption. These cytokines include interleukin (IL)-1, IL-6, and transforming growth factor α (**Table 2**). Locally produced PTHrP may also contribute to hypercalcemia by this mechanism.[13] In sites of bone metastases, tumor-infiltrating macrophages (not tumor cells) have been directly implicated in differentiating into osteoclast-like cells capable of lacunar bone resorption.[14] This differentiation may be induced by tumor-released cytokines.

Some neoplasms may secrete the active form of vitamin D, producing an elevation in serum $1,25(OH)_2D$ and causing hypercalcemia; these include MM, Hodgkin's and non-Hodgkin's lymphoma, and rarely solid tumors.[15,16] Hypercalcemia with an elevated calcitonin level is also seen in granulomatous diseases like sarcoidosis, tuberculosis, and berylliosis. Calcitriol causes increased gastrointestinal absorption of calcium and bone resorption, which is associated with decreased urinary excretion of calcium and increased renal tubular phosphate reabsorption. Although vitamin D $(1,25\ [OH]_2D)$ may be elevated in patients with PHPT, this has not been shown to be the case in patients with humoral HCM.[17]

Table 2. Tumor-Associated Osteoclast-Activating Factors

Transforming growth factor α
Interleukin-1
Interleukin-6
Tumor-derived hematopoietic colony stimulating factor
Tumor necrosis factor (especially lymphotoxin)
Vascular cell adhesion molecule-1
Hepatocyte growth factor
Prostaglandin E

Table 3. Clinical Manifestations of Hypercalcemia of Malignancy

Symptoms	Signs
General	
Fatigue, lethargy, pruritus	Dehydration
Cardiac	
Palpitations	Atrial arrhythmias, ventricular arrhythmia, shortened QT interval, prolonged PR interval, bradycardia
Neurologic	
Muscle weakness, confusion	Hyporeflexia, obtundation, psychosis, seizure, coma
Gastrointestinal	
Nausea, vomiting, constipation	Intestinal ileus and distension
Renal	
Polyuria	Renal failure
Skeletal	
Bone pain	Bone fracture

DIAGNOSIS

Patients presenting with asymptomatic hypercalcemia or chronic symptoms (fatigue, lethargy, and weakness) are more likely to have PHPT. Subperiosteal bone resorption, if present, is suggestive of long-standing hypercalcemia. However, if the onset of symptoms is recent (especially when symptoms involve seizure, confusion, or coma) and weight loss is a feature, then malignancy should be suspected.[1,18,19]

Calcium affects multiple organ systems, which explains the wide variety of symptoms seen in hypercalcemia (**Table 3**). The severity of these signs and symptoms is determined not only by the degree of hypercalcemia, but also by the rapidity of the rise in calcium, the patient's general health, extent of primary disease, and comorbid conditions. Nonspecific manifestations include fatigue, lethargy, and weakness. In presentations with nonspecific manifestations, the diagnosis of hypercalcemia is often made on routine blood tests. If untreated, the combination of nausea, vomiting, and polyuria may lead to severe dehydration with worsening hypercalcemia. Confusion, seizure, and coma are manifestations of hypercalcemic crisis and warrant immediate therapy. Features of the primary disease, including evidence of any bone metastases, may be present. A positive family history for PHPT should be further evaluated by a search for genetic disorders such as multiple endocrine neoplasia (type 1 and 2A).

Although the laboratory diagnosis of hypercalcemia is relatively straightforward, all efforts should be made to establish the presence of true hypercalcemia as opposed to hypercalcemia due to laboratory error or dehydration. Calcium levels should be compared with earlier values if available, and solitary or unusually high values should be repeated. Because approximately 40% of calcium is bound to proteins (mainly to albumin), measured serum calcium must be corrected for albumin level. In hypoalbuminemic states, measured calcium level tends to underestimate the degree of hypercalcemia. For every 1 mg/dL drop in albumin below 4 g/dL, serum calcium increases by 0.8 mg/dL. Corrected calcium in mg/dL therefore can be estimated as follows:

$$\text{Corrected calcium} = \text{measured total Ca (mg/dL)} + 0.8\,(4.0 - \text{serum albumin [g/dL]})$$

Conversely, calcium-binding myeloma proteins in MM (and paraproteinemias) may give the spurious impression of hypercalcemia.[20] For this reason, measurement of serum ionized calcium is preferred.

Hypercalcemia resulting from high levels of intact PTH (PHPT) or PTHrP (humoral HCM) is prevalent,[21,22] and patients having one disease may be at increased risk of developing the other.[23,24] Therefore, both intact PTH and PTHrP must be assayed in patients without obvious malignancy (**Table 4**). In those with established malignancy, intact PTH still should be checked to assess whether coexistent PHPT is present. Pure HCM is associated with a low PTH level, and in patients with this finding, performing an assay for PTHrP would not be necessary. Renal function should be taken into account in all patients with elevated PTH, because PTH rises exponentially with a glomerular filtration rate (GFR) below 50 mL/min. Parathyroid cancer, tertiary hyperparathyroidism, and ectopic PTH secretion (very rarely reported in ovarian and small cell lung cancers) may give rise to hypercalcemia with elevated PTH. Some patients with humoral HCM have suppressed PTHrP, while others without hypercalcemia have

Table 4. Evaluation of Hypercalcemia of Malignancy with PTH and PTHrP Levels

PTH	PTHrP	Disorder
Low or low normal	Elevated	HCM (humoral)
Elevated or high normal*	Absent	Primary and tertiary hyperparathyroidism Parathyroid carcinoma Lithium therapy Ectopic PTH (rare)
Low or normal	Absent	HCM (metastatic) Other causes of hypercalcemia (hyperthyroidism, Paget's disease in the presence of immobility)
Elevated	Elevated	Coexistent hyperparathyroidism with humoral HCM

HCM = hypercalcemia of malignancy; PTH = parathyroid hormone; PTHrP = parathyroid–related protein.

*Patients with a high normal PTH level may indeed have primary hyperparathyroidism because in primary hyperparathyroidism the level of PTH is inappropriately high for the calcium level. Measurement of mid-region PTH may be more sensitive in patients with kidney diseases than intact (complete length) PTH.[25]

elevated PTHrP,[26] emphasizing the multifactorial nature of HCM etiology. In cases of diagnostic uncertainty, measurement of serum calcidiol and calcitriol can be helpful. Granulomatous diseases and lymphomas cause hypercalcemia by stimulating the production of calcitriol.[17] In vitamin D toxicity, hepatic production of the metabolite calcidiol is increased.[27]

Specific tests for diagnosis of the primary disorder may be necessary when this has not been confirmed. Bone survey and serum protein electrophoresis may help confirm MM, chest radiography may detect lung cancer or sarcoidosis, and bone or positron emission tomography scan will show bone metastases. It is important to assess the hydration status and cardiovascular reserve of patients with hypercalcemia as high-volume rehydration may be part of the treatment plan.

TREATMENT

The management of patients with HCM depends on the severity of symptoms and the degree of hypercalcemia. In advanced cancer, careful discussion must be held with patient and family on the merits and goals of treatment. Consideration must be given to the patient's disease stage, preferences, and benefit-to-risk ratio. In severely debilitated patients, a decision not to treat hypercalcemia may be appropriate.[28] In such patients, the median survival is measured in days.[29]

When the decision to treat has been made, treatment must be carried out in a decisive and expedited manner. Furthermore, all patients with HCM should have a histologic diagnosis and staging of their disease since treatment of the underlying malignancy is necessary for maintaining normocalcemia. However, calcium levels should be stabilized before any extensive malignancy workup is commenced. Important therapeutic modalities include saline hydration, oral phosphates, salmon calcitonin, corticosteroids, bisphosphonates, gallium nitrate, and dialysis.

Mild Hypercalcemia (10.5–12 mg/dL)

Asymptomatic patients with serum calcium between 11 mg/dL and 12 mg/dL may be at increased risk for nephrolithiasis due to hypercalciuria. In the absence of severe nausea, vomiting, or polyuria, patients with mild hypercalcemia can be hydrated orally. Oral rehydration with increased salt and oral phosphate (0.5–3 g/day) is recommended (provided serum phosphate is < 4 mg/dL). Although phosphates are highly effective hypocalcemic therapy,[30] serum creatinine should be monitored regularly to avoid renal insufficiency. Phosphate therapy should be discontinued if the calcium–phosphorous product exceeds 55.[31] For patients who cannot be reliably hydrated orally due to persistent nausea and vomiting or who have significant dehydration due to polyuria and poor oral intake, admission and intravenous (IV) hydration is warranted. Uncorrected dehydration may worsen hypercalcemia, which may lead to further dehydration. Because HCM is a consequence of increased bone resorption, it is not necessary to restrict dietary calcium, but all calcium supplements should be withdrawn.[28] Furthermore, all hypercalcemic agents (lithium, vitamin D supplement, thiazide) should be discontinued, and immobilization, which leads to bone resorption, should be reduced to a minimum.

Moderate Hypercalcemia (> 12–14 mg/dL)

If serum calcium is above 12 mg/dL or the patient manifests symptomatic hypercalcemia, hospitalization is necessary and volume depletion from calcium-induced diuresis must be immediately corrected. Normal saline is administered judiciously, but care should be taken in patients with renal or heart failure. IV infusion of saline can be started at a rate of 200 to 300 mL/hr and titrated to a target urine output of 150 mL/hr and urine sodium level greater than 20 mmol/L. Volume expansion will inhibit proximal tubular reabsorption of calcium and lead to calciuresis.

Theoretically, loop diuretics block calcium reabsorption in the loop of Henle and may improve calciuresis, but there are no data supporting the routine use of loop diuretics to promote calciuresis. Furosemide may

increase the risk of hypovolemia with resultant decrease in GFR, which actually stimulates renal calcium reabsorption. Furosemide use generally should be restricted to grossly edematous patients or those with fluid overloading during therapy. Serum electrolytes (especially phosphorous, potassium, and magnesium) should be monitored in all patients, particularly during diuretic use. Hypophosphatemia should not be treated unless symptomatic. Although hypercalciuria is a desirable effect of hypophosphatemia, central nervous system effects (irritability, confusion, seizure), respiratory failure, and clinically significant heart failure may occur in patients with severe hypophosphatemia. The calcium–phosphorous product should be maintained at less than 70 to avoid calcium salt precipitation in the kidneys and soft tissues.

Calcitonin. Most oncologists do not use calcitonin in asymptomatic patients, but it may be employed as bridge therapy in very ill patients before the effects of bisphosphonates occur. The dose of calcitonin used is 4 IU/kg (intramuscularly or subcutaneously, not intranasally), and serum calcium should be checked within 4 to 6 hours after calcitonin is administered. Calcitonin interferes with osteoclast maturation and promotes calciuresis.[32] Although calcitonin's relatively rapid onset of action (4–6 hr) makes it ideal for acute management of hypercalcemia, it is a very weak agent, decreasing serum calcium by only 1 to 2 mg/dL.[33] In patients who are calcitonin-sensitive, subsequent doses can be continued at 4 to 8 IU/kg every 6 to 12 hours. Calcitonin is relatively safe except for mild gastrointestinal upset and hypersensitivity in patients with fish allergy, in whom skin testing should be considered. Calcitonin also may be associated with tachyphylaxis, limiting its long-term use.

There is evidence that combination therapy with calcitonin and corticosteroids improves response by preventing tachyphylaxis and maintaining osteoblast function.[34,35] Corticosteroids may also help lower calcium levels in patients with steroid-sensitive tumors (MM, lymphoma, and leukemia), but are generally not effective in treating hypercalcemia associated with solid tumors. The use of glucocorticoids should therefore be limited to patients who have steroid-sensitive tumors, bisphosphonate failure, calcitonin tachyphylaxis, and other indications for steroid use (eg, pain control or nausea); those who cannot tolerate bisphosphonates; and those for whom bisphosphonates are unavailable.

Bisphosphonates. IV hydration and calcitonin may control hypercalcemia within the first 48 hours, but this alone is not sufficient to maintain normocalcemia. Single-dose IV bisphosphonates in the form of zoledronic acid or pamidronate should be given as early as possible because maximum effect occurs in 2 to 4 days. Etidronate is also available in the United States, but it may induce osteomalacia.[36] They are more potent than calcitonin plus saline and therefore are considered the mainstay for hypercalcemia management. Bisphosphonates bind to hydroxyapatite crystals in bone matrix and inhibit osteoclastic bone resorption, but resistance may occur in humoral HCM because bisphosphonates do not inhibit PTHrP-induced calcium reabsorption in the kidneys.

The bisphosphonates are considered to be relatively nontoxic; hypocalcemia and renal failure seem to be the main adverse effects. In patients with borderline renal function, particular attention must be paid to hydration, use of other nephrotoxic agents, and creatinine monitoring. Bisphosphonates should only be given after adequate hydration (urine output 100 mL/hr), and dose adjustment is necessary in patients with GFR below 60 mL/min. Other (rare) side effects include flu-like symptoms, gastrointestinal upset, jaw osteonecrosis, and ocular complications such as uveitis, conjunctivitis, and episcleritis. While zoledronic acid and pamidronate both have a median duration of effect of 30 days, the former is preferred because it is at least 100 times more potent that pamidronate and is infused over 15 minutes as opposed to 4 hours.[28]

Weekly monitoring of serum calcium levels is appropriate after a bisphosphonate infusion; if hypercalcemia recurs, a repeat injection can be given. When there is evidence of resistance to a particular bisphosphonate (absence of response in 7 days or shorter duration of effect), another bisphosphonate might be given or gallium nitrate can be considered.

Gallium nitrate. Unlike bisphosphonates, gallium nitrate inhibits PTHrP-mediated hypercalcemia in addition to PTH-associated hypercalcemia. It preferentially accumulates in metabolically active bone, where it reduces bone resorption by decreasing acid secretion by osteoclasts through an ATPase-dependant proton pump.[37] It is given as an IV infusion over 5 days at a dose of 100 to 200 mg/m^2/day. Gallium nitrate is more potent than pamidronate. Common side effects include gastrointestinal upset, confusion, hallucination, and lethargy. More serious but rare side effects can occur and include nephrotoxicity, hypotension, hypocalcemia, hypomagnesemia, hypophosphatemia, and respiratory alkalosis. Due to considerable side effects and a 5-day infusion period, gallium nitrate is not widely used. Plicamycin is another hypocalcemic agent that is no longer used due to side effects.

Severe Hypercalcemia (> 14 mg/dL)

In rare cases, patients may present with serum calcium levels at or above 14 mg/dL and severe symptoms of hypercalcemia. The measures discussed previously should be pursued aggressively while arrangements are made for urgent dialysis. Low calcium or calcium-free dialysate is used. Dialysis is also the modality of choice in patients who cannot receive large volumes of IV fluids due to fluid overload states.

Future Trends

Noncalcemic analogs of calcitriol are substances that maintain the suppressive action of $1,25(OH)_2D_3$ on parathyroid gland with very little calcemic activity. Currently, the vitamin D analogs 1 alpha$(OH)D_2$ and 19-nor $1,25(OH)_2D_2$ are available for the treatment of secondary hyperparathyroidism in chronic renal failure, while oxacalcitriol is currently under review.[38] The low calcemic activity of oxacalcitriol combined with its ability to selectively inhibit the release of PTHrP makes it ideal for HCM treatment. Immunotherapy with PTH peptides is another area of interest. In a patient with severe hypercalcemia resistant to conventional therapy, an injection of bovine and human PTH peptides with booster doses at weeks 4 and 11 stimulated the production of PTH antibodies, causing a precipitous decline in serum calcium.[39]

Prevention

Bisphosphonates can be used in the prevention of humoral HCM, pathologic fractures, bone pain, and spinal cord compression in patients with cancer and documented bone metastases. However, data from a study involving women with stage IV breast cancer on cytotoxic therapy reported a statistically insignificant survival benefit from pamidronate therapy (14.8 mo versus 14.2 mo) when compared with placebo.[40]

PROGNOSIS

The prognosis of patients with HCM is uniformly poor. In one study, nearly 50% of patients with HCM died within 30 days of commencing treatment, and within 3 months, up to 75% of these patients died.[29] Serum levels of PTHrP can be used to prognosticate. Elevated PTHrP predicts shorter median survival[41] and bisphosphonate failure.[42] It also can be used as a tumor marker to monitor response to both tumor and hypercalcemia therapy.[43]

SUMMARY

HCM is the most common metabolic emergency associated with cancer. It carries a poor prognosis, and by the time HCM is diagnosed most patients have advanced malignant disease. Although PHPT is the most common cause of hypercalcemia in general, HCM is the most likely cause of hypercalcemia in hospitalized patients. Most HCM cases are due to the effect of hormonal factors (PTHrP and calcitonin), and thus are called humoral HCM. Additionally, local osteolysis due to bone metastases may contribute to hypercalcemia in certain malignancies. Although the symptoms are nonspecific and may be attributed to the underlying disease or its treatment, the diagnosis of HCM can be readily established from a routine basic metabolic profile. Ionized calcium should be measured, but when it is not, corrected calcium can be estimated arithmetically. In severe HCM, the benefits of therapy should be weighed against a patient's general clinical condition. If treatment is agreed upon, admission to the intensive care unit may be necessary; aggressive IV hydration and bisphosphonate therapy are the mainstay of treatment. In very ill patients, calcitonin may be used as bridge therapy before the effect of bisphosphonate sets in. Glucocorticoids should be reserved for steroid-responsive tumors. **HP**

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