Humoral Hypercalcemia of Malignancy

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Contents

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Opening

Hypercalcemia is a quite common metabolic complication in cancer patients. The severe form of hypercalcemia could be a life-threatening condition, requiring immediate medical intervention. In this chapter, the endocrine form of malignancy-related hypercalcemia, that is humoral hypercalcemia of malignancy, will be discussed – that is the most common form of malignancy-related hypercalcemias. The management of hypercalcemia is also presented in this chapter.

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Definition of the Disease

The diagnosis of hypercalcemia is confirmed if the serum calcium level is above the upper limit of the normal reference value (normal total serum calcium: 2.2–2.6 mmol/L or 8.82–10.62 mg/dL). Hypercalcemia affects approximately 20–30% of all cancer patients during the course of the disease. A positive cancer history could help in the diagnosis of malignancy-associated hypercalcemia (MAH), but hypercalcemia could also be the first sign of the disease. Malignancy-associated hypercalcemia is divided into four groups (Table 49.1):

1. *Humoral hypercalcemia of malignancy (HHM)* that is caused by the secretion of mainly Parathyroid Hormone-Related Protein (PTHrP) by several different malignancies including renal cancer, ovarian cancer, breast cancer, or squamous cell carcinomas of the lung, head, and neck cancers, esophagus cancer, and so on. The onset of hypercalcemia is usually associated with an advanced stage of the underlying malignant disease. The prognosis is poor, as the life expectancy does not exceed 6 months in the majority of the cases, and approximately 50% of patients decease within 30 days after diagnosis.

   PTHrP has high homology with parathyroid hormone and shares the same receptor. In normal conditions, however, PTHrP is mainly a local, paracrine mediator that does not have a role in the regulation of normal calcium homeostasis. The uncontrolled secretion of PTHrP by a malignant tumor as a form of a paraneoplastic endocrine syndrome leads to hypercalcemia.
2. *Local osteolytic hypercalcemia (LOH)*, that is due to metastatic bone destruction, for example, in multiple myeloma or breast cancer.
3. *Excessive 1,25-dihydroxyvitamin D (calcitriol) secretion*, observed in some types of lymphomas.
4. *Ectopic parathyroid hormone (PTH) secretion*, that is very rare.

The chapter discusses HHM, which is the most common form accounting for approximately 80% of all MAH. PTHrP elevates the serum calcium level by increasing bone resorption and enhancing the renal resorption of calcium like parathyroid hormone.

Table 49.1 Forms of malignancy-related hypercalcemias

Type of hypercalcemia	Frequency (%)	Typical related malignancies
Humoral hypercalcemia of malignancy (HHM)	80	Squamous cell carcinomas (esophageal, lung, head and neck, cervix) Breast, renal, bladder, ovarian, prostate, and colorectal cancer Hematological malignancies
Local osteolytic hypercalcemia (LOH)	20	Breast cancer Multiple myeloma Lymphoma
Excessive 1,25-dihydroxyvitamin D secretion	<1	Lymphoma
Ectopic parathyroid hormone (PTH) secretion	<1	Variable

Case Report

The 57-year-old female patient was diagnosed with a malignant tumor in her left breast. Preoperative staging (abdominal ultrasound, chest X-ray, bone scan) did not reveal distant metastases. The patient was operated: lumpectomy and sentinel lymph node biopsy were performed. The pathological diagnosis was an invasive ductal adenocarcinoma, pT2 (40 mm), ER (estrogen receptor): negative, PR (progesteron receptor): negative, HER2: +++, Ki-67: ~15%. Based on the pathological results, adjuvant chemotherapy and trastuzumab were indicated. Two cycles of epirubicin + cyclophosphamide combination were given. Before the third cycle, the patient was hospitalized because of weakness, constipation, nausea, and abdominal pain. Clinical findings at hospitalization: blood pressure 150/80 mmHg, HR 84/min, normal temperature, and mild dizziness.

What are the signs and symptoms of hypercalcemia?

Two main factors have significant role in the development of a symptomatic hypercalcemia: the level of serum calcium and the rapidity of its development. Hypercalcemia is severe if total serum Ca is >3.5 mmol/L (>14 mg/dL), whereas it is life-threatening over 4 mmol/L (>16 mg/dL). The suspicion of hypercalcemia should be based on clinical symptoms. Patients often complain about fatigue and anorexia. Clinical symptoms regularly affect four organ systems.

1. The neurological symptoms include muscle weakness, behavioral changes, disorientation, somnolence or coma, and posterior reversible leukoencephalopathy. A rapid increase of the serum calcium level frequently leads to severe neurologic dysfunction, while a chronic hypercalcemia could result in moderate symptoms.

2. The renal involvement could lead to acute kidney injury, nephrogenic diabetes insipidus, renal vasoconstriction, and distal renal tubular acidosis with consequential polyuria. The polyuria, along with the reduced fluid intake caused by the gastro-

Table 49.2 Clinical manifestation of hypercalcemia

Organ	Dysfunction
Cardiovascular	Arrhythmias, short QT interval, ST abnormalities, hypertension
Gastrointestinal	Nausea, vomiting, peptic ulcer disease, constipation, and acute pancreatitis
Neuropsychiatric	Behavioral changes, disorientation, somnolence or coma, posterior reversible leukoencephalopathy
Renal	Nephrolithiasis, acute kidney injury (nephrogenic diabetes insipidus with consequential polyuria), chronic renal insufficiency

intestinal symptoms, leads to severe fluid depletion that further aggravates hypercalcemia.

3. Gastrointestinal symptoms include nausea, vomiting, peptic ulcer disease, constipation, and in severe cases even acute pancreatitis.

4. Cardiovascular alterations include arrhythmias, short QT interval, ST abnormalities, and hypertension. The clinical symptoms are summarized in Table 49.2.

Case Report Continued

At the time of hospitalization, the patient's laboratory results were found as follows: serum calcium 4.9 mmol/L, serum BUN (blood urea nitrogen): 11.9 mmol/L (normal 2.8–7.2); creatinine: 177 μmol/L (normal: 59–104); Glomerular filtration rate (GFR): 26.9 ml/min/1.73 m2 (normal >90). Liver function was not altered, and no anemia, only a mild thrombocytopenia was observed. During the next 3 days, despite proper treatment her kidney function worsened, and hypercalcemia persisted. Abdominal ultrasound did not show any sign of metastatic intraabdominal spread. Thoracic radiography was also negative. Parathyroid hormone (PTH) level was low 8.7 pg/mL (normal range: 15.0–65.0) and 25-hydroxyvitamin-D was within the normal range. Serum albumin as well as the total serum protein levels were normal.

What kind of laboratory measurements should be performed?

Total serum calcium should be measured in any case of the clinical suspicion of hypercalcemia. Total serum calcium is a sum of two different forms. The free or ionized calcium is the physiologically active part (approx. 45–50%), while the other proportion is bound to carriers. The major carriers for calcium are proteins (approx. 40%) mostly albumin, while only a small proportion is bound to globulins. About 10–15% is bound to organic or inorganic anions. Any condition which influences the serum albumin level will also influence the total calcium levels. Hypoalbuminemia is frequent in cancer patients, therefore, it is strongly recommended to calculate the corrected total calcium level in these cases (see next question). There are several online formulas available. The measurement of free, ionized calcium level is another option.

The level of the PTH should also be routinely measured, since it is needed for the diagnosis of HHM, moreover, concomitant primary hyperparathyroidism is relatively frequently found in cancer patients and it is not associated with poor prognosis. 25-Hydroxyvitamin-D should be measured to exclude vitamin D-mediated hypercalcemia. The routine laboratory measurement, including renal function, blood count, and serum phosphorus level could help in treatment planning and monitoring.

How to correct serum calcium for alterations of serum albumin concentrations?

Any 10 g/L (1 g/dL) decrease in serum albumin concentration reduces the measured total calcium by 0.2 mmol/L (0.8 mg/dL). Therefore, 0.2 mmol/l (0.8 mg/dL) should be added to the measured total calcium for correction. For example, if the albumin levels are reduced by 20 g/L than the normal value, then 2 × 0.2 mmol/L (2 × 0.8 mg/dL) should be added to the measured serum calcium. (The other direction is also valid if hyperproteinemia is present.)

How can we differentiate between the various forms of hypercalcemias?

It should be kept in mind that despite the proven, advanced malignant disease, primary hyperparathyroidism must be excluded, as we discussed above. PTH measurement plays a key role in differential diagnosis. Elevated PTH level refers to primary hyperparathyroidism in most of the cases, but very rarely some tumors might also secrete PTH as an ectopic hormone. In case of normal or suppressed level of PTH (<20 pg/mL) and a proven diagnosis of an advanced solid tumor, the diagnosis of HHM can be established, and the measurement of PTHrP is not always required. The use of certain medications often given to cancer patients could also be related to hypercalcemia (thiazide diuretics, estrogens, tamoxifen, aminophylline, lithium, vitamins A-, and D); therefore revision of the concomitant medication is essential.

What kind of treatment options for hypercalcemia are available?

In case of severe, life-threatening hypercalcemia, the first step is volume expansion with intravenous saline infusion, at a rate of 200–300 mL/hour. After achieving proper rehydration (urinary excretion 100–150 mL/hour), calcitonin treatment is recommended at a dose of 4 IU/kg, intramuscularly or subcutaneously. The level of calcium should be carefully monitored, since not all patients are calcitonin sensitive. In case of detectable response, the calcitonin administration could be repeated every 6–12 hours. (Many years ago, calcitonin was widely used in the treatment of osteoporosis, but with the advent of more effective drugs, it is rarely used nowadays. In the treatment of acute hypercalcemia, calcitonin is effective as a rapidly acting drug.)

Intravenous bisphosphonates are very effective in reducing calcium levels, but they do not act very rapidly. Either zoledronic acid (4 mg) or pamidronate (60–90 mg) should be recommended. Zoledronic acid seems to be superior to pamidronate in reversing hypercalcemia. Ibandronate is also a therapeutic option. In case of severe renal impairment, bisphosphonates are contraindicated and therefore denosumab (a monoclonal antibody against RANKL (receptor activator of nuclear factor kappa-B ligand) inhibiting osteoclast activation) is another effective medical treatment.

Patients diagnosed with renal or heart failure should also be treated with loop diuretics (e.g., furosemide). Therapy refractory hypercalcemia accompanied with severe renal failure could be an indication for hemodialysis. Recovery is expected in 2–4 days after the initiation of therapy, but recurrence is very likely. Since the recurrence of hypercalcemia correlates with the progression of underlying disease, the initiation of proper anticancer treatment is also important. Patients with mild or asymptomatic hypercalcemia do not require immediate medical therapy.

Case Report Follow-Up

After 4 days of treatment, our patient started to recover and was discharged from the hospital after a week. As a summary of her history, primary hyperparathyroidism was excluded, since the level of PTH was below the normal. HMM was the most likely reason of the hypercalcemia, therefore, more precise restaging was recommended, since at the onset of the hypercalcemia there was no sign of an advanced disease. PTHrP levels can be measured for confirming the diagnosis.

What kind of imaging should be performed?

At the onset of a clinically significant hypercalcemia, the underlying malignant disease is usually already confirmed in the majority of cases. CT and/or magnetic resonance imaging (MRI) scans are considered as part of the regular staging procedures in cancer patients. Bone scan and ^{18}fluorodeoxyglucose-positron emission tomography-computed tomography (^{18}FDG-PET-CT) are both useful in detecting potential osseal metastases. Bone metastases should be excluded for confirming the diagnosis of MAH.

Case Report Continued

After recovering from hypercalcemia and having been discharged from the hospital, an ^{18}FDG-PET-CT was performed. It showed an advanced disease, as multiple small liver and lung metastases were seen. There was still no sign of bone metastases. Proper first line anticancer therapy was initiated, per protocol with a taxane and trastuzumab combination, but after 4 months, disease progression was observed. We lost our patient in 6 months.

Tips

The reader is advised to read the chapter on primary hyperparathyroidism (▶ Chap. 22) and also the chapter on osteoporosis (▶ Chap. 24) as drugs used in the treatment of hypercalcemia overlap with antiporotic medications.

Take Home Messages

- Severe hypercalcemia is a life-threatening complication.
- Humoral hypercalcemia of malignancy (HHM) is the most frequent form of malignancy-related hypercalcemias.
- In the absence of osseal metastases, the diagnosis of HMM is usually established if the level of PTH is normal or suppressed (<20 pg/mL), and the diagnosis of advanced malignant disease is already proven. PTHrP can also be measured.
- Fluid replacement, calcitonin, and bisphosphonates are the most important treatment options.
- Recurrence of hypercalcemia is very likely, as it is associated with the progression of the underlying malignant disease.
- The prognosis of hypercalcemia is poor, 50% of the patients die in 30 days, and the life expectancy is no more than 6 months.

Suggested Reading

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