Cancer and Hypercalcemia; a Review of the Diagnosis and Treatment Through an Unusual Case

Kanser ve Hiperkalsemi; Nadir Görülen bir Vaka Aracılığı ile Tanı ve Tedavinin Gözden Geçirilmesi

Alper Ata, Tolga Köşeci*, Ali Arıcan**
Mersin State Hospital, Department of Medical Oncology, Mersin, Turkey
*Mersin University Medical Faculty, Department of Internal Medicine, Mersin, Turkey
**Mersin University Medical Faculty, Department of Oncology, Mersin, Turkey

Abstract
Here, we present a 45-year-old woman with endometrial cancer who presented with hyperemesis, vomiting and loss of consciousness. The serum calcium concentration was 18.3 mg/dl and bone scintigraphy revealed no evidence of skeletal involvement by the tumor. Her parathyroid hormone (PTH) level was normal, but the parathyroid hormone-related peptide (PTHrP) level was higher than the normal values. Through our case, we review the treatment of malignant hypercalcemia. Turk Jem 2013; 17: 8-11

Key words: Hypercalcemia, endometrium adenocancer

Introduction
Humoral hypercalcemia related to malignancy is a frequently seen paraneoplastic syndrome which affects more than 10% of patients with solid tumors (1). Hypercalcemia can occur in nearly 20-30% of cancer patients at any stage of the malignancy (2-5). It may present with mental problems progressing to a comatous state and deterioration in renal functions. These symptoms are more frequently observed especially in patients during the terminal stage of their diseases. Half of these patients die within 30 days after the development of hypercalcemia (6). Hypercalcemia is usually associated with increases in both osteoclastic activity, parathormone-related peptide (PTHrP) and 1,25-dihydroxyvitamin D (1,25(OH)2D) secretion from cancer cells, and ectopic hyperparathyroidism.

Many types of cancer can cause hypercalcemia. In its diagnostic workup, measurement of serum ionized calcium (corrected for the albumin level), and serum total calcium concentrations has a critical importance. Rarely, hypercalcemia is observed in association with endometrial cancer (7-9).

Case
A 45-year-old female patient was referred to the Department of Obstetrics and Gynecology because of abnormal uterine bleeding. Histopathological examination of the samples obtained from endometrium pointed to a malignant etiology, and then she had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy with the initial diagnosis of endometrial cancer.
Surgical material was sent to the pathology laboratory, and the diagnosis was reported as endometrial adenocarcinoma (Figure 3). Twenty days after her discharge from the hospital, she was admitted to the emergency service with complaints of vomiting, nausea, and impaired consciousness. On admission, her biochemical test results were as follows: serum calcium: 18.3 mg/dl (4.5 mmol/L), serum phosphorus: 4.2 mg/dl, serum BUN: 76.4 mg/dl, serum creatinine: 2.2 mg/dl, serum albumin: 3.1 g/dl, total bilirubin: 4.2 mg/dl, direct bilirubin: 1.8 mg/dl, oxygen saturation: 92%, hemoglobin: 10.1 g/dl, platelet counts: 193,000/µl; urinalysis: bilirubin (+), protein (+), 10 RBC, a few calcium oxalate crystals and trace number of gram-positive bacteria. The patient was hospitalized in the medical oncology department with the initial diagnosis of malignant hypercalcemia.

Her physical examination (PE) findings were as follows: body temperature: 37°C, pulse rate: 90 bpm, blood pressure (left brachial): 135/70 mm Hg, and impaired consciousness, confusion, pale and icteric skin without rash or lymphadenopathy (LAP). Breath sounds were decreased at basal segments of the lungs. Normal heart sounds were auscultated. Distended abdomen and intraabdominal ascites were detected. Signs of peripheral pitting (+++) edema were seen.

There were normal shaped and sized kidneys and no nephrocalcinosis on ultrasound examination. On contrast-enhanced chest computed tomography (CT), a few mediastinal lymph nodes, and multiple nodular lesions consistent with metastatic disease were found in both lungs (Figure 1). On contrast-enhanced abdominopelvic CT, hepatomegaly, and lesions compatible with multiple hepatic metastases were noted (Figure 2). Cerebral magnetic resonance imaging (MRI) findings were not remarkable. The results of mammography, and whole-body scan were normal. Bone scintigraphy was planned, but could not be carried out because of her poor performance status. HbsAg positivity of unknown duration was detected. Levels of HBV DNA (687 IU/L), parathormon (PTH) (155 pg/ml; reference range: 15-65 pg/ml), and PTHrP (3500 pmol/dl, reference range, 13.8-55.3 pmol/dl) were also determined. Histopathologic results of biopsy samples taken from hepatic nodular lesions were consistent with a metastatic adenocarcinoma lesion. Physiologic saline infusion was started (200-300 ml/hr IV) with presumptive diagnosis of malignant hypercalcemia. The patient also received dialysis therapy at 12 hour-intervals for 2 times. Following dialysis, intravenous bisphosphonate (3 mg zoledronic acid, 25% dose reduced) therapy was started. After hydration of the patient, 40 mg IV furosemide was started. Following these treatments, serum calcium level of the patient decreased to 12.5 mg/dl (concurrent serum values of albumin, BUN, and creatinine were 2.8 g/dl, 80.2 mg/dl and 2.5 mg/dl, respectively). During follow-up period, her calcium values rose again (calcium, 14.8 mg/dl; albumin, 2.8 mg/dl) which additionally necessitated administration of calcitonin 200 IU s.c. bid, and 80 mg methylprednisolone once daily. However, her calcium levels did not return to normal levels, on the contrary, they steadily peaked (calcium 14.2 mg/dl, albumin 2.7 g/dl). General health state of the patient deteriorated further. PE revealed tachypneic and hyperpneic breathing patterns, and her electrocardiogram (ECG) demonstrated signs of sinus tachycardia. Her blood pressure was 80/50 mmHg. The patient developed respiratory, and then, cardiac arrest. She was intubated, and cardiopulmonary resuscitation was attempted. She responded to cardiopulmonary resuscitation. She was then connected to the mechanical ventilator for one day, but she was passed away on the 17th day of her hospitalization.

**Discussion**

Hypercalcemia of malignancy is observed in nearly 20-30% of cancer patients (10). Hypercalcemia is most frequently seen in malignancies...
such as breast cancer, lung cancer, and multiple myeloma. Development of hypercalcemia in cancer patients is generally a sign of poor prognosis, and approximately 50% of the patients die within 30 days of its onset (9). Our patient also lost her life 17 days after the detection of hypercalcemia. Mainly 3 factors are responsible for hypercalcemia occurring in cancer patients. Osteolytic metastases; develop as a result of cytokine release which induces secretion of osteoclast activating factor which are responsible for nearly 20% of hypercalcemia cases in cancer patients (3,5,10,11). Release of PTHrP comprises nearly 80% of hypercalcemia cases (malignancy-related humoral hypercalcemia) associated with malignancies (3,12-14). Finally, less frequently, hypercalcemia might develop depending on the production of vitamin D by cancer cells. In our case, PTH and vitamin D levels were within normal limits at two separate measurements, however, PTHrP levels were 70 times higher than the upper limit of the normal value. Humoral hypercalcemia associated with malignancies is characterized by higher serum calcium levels without bone metastases, and increased PTH levels (15). Generally, squamous cell carcinomas are implicated for malignancy-related humoral hypercalcemia which is rarely associated with adenocarcinomas (16). In these patients, PTH level is suppressed because of increased PTHrP levels. PTHrP increases release of calcium from bones, and accelerates renal tubular absorption of calcium leading to hypercalcemia (14,17-19). PTHrP release is mostly observed in renal cell carcinoma, ovarian cancer, and breast cancers. Rarely, PTHrP increases in endometrial cancers, and only a few cases have been reported in the literature so far (7-9).

Patients with a serum calcium level below 12 mg/dl are usually asymptomatic, and this condition is termed as mild hypercalcemia. If serum calcium value is between 12 and 14 mg/dl, then it is called moderate hypercalcemia which can be tolerated well, but sudden increases in calcium levels might lead to the emergence of symptoms as polyuria, and polydipsia. If serum calcium is above 14 mg/dl or over, then it is termed severe hypercalcemia. In severe hypercalcemia, multisystem symptoms can be observed as follows: neurologic symptoms: stupor, coma, confusion, and lethargy; gastrointestinal symptoms: constipation, peptic ulcus and pancreatitis, urinary symptoms: nephrolithiasis, renal failure, and nephrogenic diabetes insipidus (17-20). Besides muscle weakness (21), cardiomyopathy, calcification of heart valves (17,20,21) and arrhythmias can be seen (18). On admission, since our patient’s serum calcium level was 18.3 mg/dl, she was considered to be severely hypercalcemic patient.

Patients who become hypercalcemic secondary to a malignancy are usually dehydrated. Causes of dehydration include natriuresis, nausea-vomiting and poor oral intake. Therefore, in the treatment of these patients, hydration should be applied as a first measure. Hydration accelerates glomerular filtration rate resulting in increased passage of calcium into tubular lumen. Besides, saline infusion has itself a calcieuretic effect. Diuretics can be used in the treatment of hypercalcemia. Because of their accelerating effects on renal clearance of calcium, loop diuretics are preferred at daily doses of 20-40 mg. However, diuretic therapy should be started after adequate hydration is ensured.

Bisphosphonates can be used in the treatment of severe hypercalcemia. It should not be forgotten that bisphosphonates become effective within 2-4 days of the treatment (22,23). Calcitonin manifests its effectiveness by increasing renal clearance of calcium, and preventing calcium resorption from bones (24,25). Generally, it is administered at the dosage of 4-8 IU/kg IM or SC at 12-hour intervals. Calcitonin nasal sprays are not very effective (26). Therefore, we administered calcitonin via subcutaneous route unfortunately without any decrease in serum calcium levels. Glucocorticoids at daily doses of 60 mg can be used in cases refractory to hydration, bisphosphonate, and diuretic therapy (27,28). However, our patient did not respond well to glucocorticoid therapy, either.

Hemodialysis can be used in severe hypercalcemia. Especially, if glomerular filtration rate drops below 10-20 ml/min secondary to hypercalcemia or in the presence of heart failure where hydration is contraindicated, hemodialysis might be an alternative (29).

In summary, PTHrP-dependent hypercalcemia comprises 80% of malign hypercalcemias. PTHrP is mostly released from squamous cell carcinomas, and rarely from adenocarcinomas. Particularly, PTHrP release associated with endometrial carcinoma is very rarely observed. In this case report, we investigated hypercalcemia which occurred in a patient with endometrial adenocarcinoma, and after eliminating other causes, we determined higher PTHrP levels as an underlying cause of hypercalcemia. Despite all therapeutic modalities we applied, we could not correct hypercalcemia. In all cancer patients, it should not be forgotten that hypercalcemia is a serious and frequently seen paraneoplastic syndrome, and every patient should be monitored closely in consideration of this entity.

References


