A Different Cause of Malignant Hypercalcemia in a Breast Carcinoma with Bone Metastasis

Kemik Metastazı Olan Meme Kanserli Bir Hastada Malign Hiperkalseminin Farklı Bir Nedeni


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Abstract

Hypercalcemia refers to a condition of calcium levels in blood above the normal range. Most common causes of hypercalcemia include overactivity of parathyroid glands, also known as primary hyperparathyroidism (PHPT), and malignancies. These two disorders contribute to 90% of etiologies leading to hypercalcemia. Various types of cancer manifest hypercalcemia, including breast carcinoma, lung carcinoma, and multiple myeloma. For instance, hypercalcemia is observed in 30% to 40% of patients with breast cancer. The occurrence of hypercalcemia in cancers is attributed to bone metastasis and paraneoplastic syndromes. Malignancies may also be accompanied by PHPT. Therefore, in cancer patients with hypercalcemia, serum parathyroid hormone (PTH) level should be assessed. In the present study, we present a case of breast cancer with hypercalcemia to emphasize the role of PHPT in malignancies.

Keywords: Breast cancer; hypercalcemia; positron emission tomography; primary hyperparathyroidism

Özet


Anahtar kelimeler: Meme kanseri; hiperkalsemi; pozitron emisyon tomografisi; primer hiperparatiroidizm

Introduction

The most common causes of hypercalcemia are Primary Hyperparathyroidism (PHPT) and malignancies. These two disorders cover 90% of etiologies leading to hypercalcemia (1). The cancers where hypercalcemia is mostly seen are breast carcinoma, lung carcinoma, and multiple myeloma. Hypercalcemia is observed in 30-40% of breast cancer patients (2). Breast carcinoma is most frequent cancer in women and the second cause of death after lung cancer. The most frequent causes of hypercalcemia in cancer patients are bone metastasis and paraneoplastic syndromes (1–4). Malignancies might also be found with PHPT. Therefore, in cancer patients with hypercalcemia, serum parathyroid hormone (PTH) level should be assessed (5). We present this case in order to further emphasize the fact that PHPT might accompany malignancies.
Case Report

A 37-year-old female patient was admitted to our medical oncology center nearly three months ago with a mass in the left breast and left axilla. Ultrasonographic examination of the breast revealed a 2.5-cm mass lesion with irregular contoured microcalcifications. Pathological examination of tru-cut biopsy revealed invasive ductal carcinoma. Positron emission tomography-computed tomography (PET-CT) was conducted that revealed a multi-centric tumor in the left breast, metastatic lymph nodes in left axilla, and a lytic metastatic lesion in the eighth thoracic vertebra (T8) (Figure 1A). The patient underwent modified radical mastectomy combined with axillary lymph node dissection at another center. The postoperative pathologic examination of the patient showed estrogen receptor (ER), negative; progesterone receptor (PR), 35% moderately positive; and c-erb-2, 3 positive (+) invasive papillary carcinoma. Thus, the patient was diagnosed with metastatic left breast carcinoma (T3N3M1, bone metastasis). At admission, the patient presented with weakness, loss of appetite, and weight loss. Physical examination revealed a blood pressure of 110/70 mmHg, heart rate of 88/min, respiratory rate of 18/min, and body temperature of 36.8°C. Operation scars were present in left breast and left axilla. Initial examinations revealed a hemoglobin (Hb) level of 11.1 g/dL (13.6–17.2); white cells, 7,000 mm$^3$ (5,200–12,400 mm$^3$); creatinine, 0.9 mg/dL (0.6–1.3 mg/dL); calcium, 12.4 mg/dL (8.8–10.6 mg/dL); and phosphate, 2 mg/dL (2.5–4.5 mg/dL). Magnetic resonance imaging (MRI) verified bone lesion seen in PET-CT. The lesion at T8 found in the thoracic vertebrate MRI with contrast was considered metastasis, and hypercalcemia was predicted to be related to bone metastasis. The treatment consisted of chemotherapy with docetaxel (80 mg/m$^2$/d) + trastuzumab (8 mg/kg loading dose on day 1) followed by 6 mg/kg on day 1 every 21st day. For bone metastasis, treatment comprised zoledronic acid (4 mg/every 21st day). During chemotherapy, follow-up calcium values were between 12.0 and 12.5 mg/dL; no symptom due to hypercalcemia was observed. PET-CT was used to evaluate the response to therapy after six cure chemotherapy; it revealed metastasis in the eighth thoracic vertebra. Further, diffusely increased F-18 Florodeosiglukoz (FDG) uptake by the skeletal system was noted, particularly by all costo-chondral junctions, sternum, and iliac bones as signs of a metabolic bone disorder (Figure 1B). Due to a pre-diagnosis of PHPT, PTH and 25-OH vitamin D3 levels were measured: PTH was 1,256 pg/mL (15–65 pg/mL), and 25-OH vitamin D3 was 28.6 ng/mL (20-100 ng/mL). Parathyroid ultrasound (USG) examination revealed a 25 × 16-mm hypoechoic parathyroid lesion in the inferior right thyroid lobe. The Tc-99m methoxyisobutyl isonitrile (MIBI) scintigraphy further reported it to be parathyroid adenoma (Figure 2). Thus, hypercalcemia in the patient was attributed to parathyroid adenoma, for which ultrasonographic laser ablation and percutaneous ablation alternatives were suggested. Surgery was performed after knowing patient’s preference. Postoperative pathological diagnosis was parathyroid adenoma. After parathyroid surgery, PTH and calcium levels returned to normal values.

Literature Review and Discussion

Hypercalcemia is a life-threatening electrolyte disorder. Its detection in a patient with breast cancer suffers from poor prognosis, primarily because the presence of hypercalcemia usually indicates skeletal metastasis (4). The occurrence of malignancy-associated hypercalcemia depends on three mechanisms, namely the production of local cytokines due to osteolytic metastasis (osteoclast activating factors), the secretion of parathyroid hormone-related protein (PTHrP) by tumor cells, and the synthesis of 1,25-dihydroxyvitamin D (calcitriol) by tumor cells (1). In patients with non-metastatic solid tumors, PTHrP is the most common cause of hypercalcemia (3,5,6). However, since in most patients with hypercalcemic malignancy, cancer is clinically proven, the measurement of PTHrP levels is not required. Binding of PTHrP to PTH receptors results in various biological properties of PTH. Breast cancer cells upon metastasis cause the bones to synthesize PTHrP more frequently than soft tissue tumors or primary tissue tumors. The resulting osteolysis can be cured by administration of anti-PTHrP antibodies, leading to a rise in serum calcium levels, which, in turn, is associated with morbidities related to hypercalcemia (3). Primary hyperparathyroidism is an autonomous disorder that occurs due to excessive secretion of PTH from parathyroid glands. Of primary hyperparathyroidism (PHPT), 80 to 85% depends on a single parathyroid adenoma (7). PHPT is common in cancer patients. Also, the incidence
The coexistence of PHPT with certain malignancies, including breast cancer, is still unknown (8). Since PHPT may accompany cancer cases, PTH levels should be measured in cancer patients with hypercalcemia. A high serum level of both PTHrP and PTH indicates PHPT besides malignancy. In mild hypercalcemia, PHPT should be first taken into account; if acute and severe hypercalcemia is present, hypercalcemia related to malignancy should be considered. In cases where serum PTH is high and PTHrP is low, hypercalcemia is attributed to PHPT (3). In our patient, PTH was high but PTHrP was not assessed. The 18 F-FDG PET-CT scanning is an effective and highly specific method in tumor staging, re-staging in recurrent metastatic disease, and follow-up of response to therapy in breast cancer (9). It

Figure 1: Maximum intensity projection (MIP) images of two different 18 F-FDG PET/CT scanning that was performed for staging and evaluation of response to the therapy in a patient with breast cancer. The first MIP image demonstrates increased F-18 FDG uptake in tumor tissue, axillary metastatic lymph nodes, and bone metastasis in the eighth thoracic vertebrae (black arrow) (A). Second 18 F-FDG PET/CT MIP image reveals metastasis in eighth thoracic vertebrae (black arrow) beside diffusely increased F-18 FDG uptake at skeletal system, particularly at all costochondral junctions, sternum and iliac bones as signs of a metabolic bone disorder (B).

Figure 2: Tc-99m MIBI parathyroid scintigraphy demonstrating parathyroid adenoma in the inferior of right thyroid lobe.
also contributes to the evaluation of non-oncological pathologies as in the case presented. However, 18 F-FDG PET-CT scans must be evaluated with caution so that benign cases are not mistakenly reported as metastasis. In our case, the cause of hypercalcemia was first considered as bone metastasis related to breast cancer. However, since signs of a metabolic bone disorder were observed in second 18 F-FDG PET-CT, biochemical analysis and imaging were performed, and a parathyroid adenoma was found as the cause of hypercalcemia. Clinical presentation of hypercalcemia include gastrointestinal (nausea, vomiting, abdominal cramp, pancreatitis, peptic ulcer), neuro muscular-psychiatric (attention and memory deficits, lethargy, confusion, coma), renal (nephrolithiasis, diabetes incipitus, nephrocalcinosis, dehydration, renal insufficiency), cardiovascular (hypertension, arrhythmia, short QT), and bone symptoms (pain, cystitis fibrosis). Additionally, weight loss might be observed in accordance with the etiology (10). None of these were present in our patient. The laboratory results play a key role in determining the severity and etiology of hypercalcemia. Hypercalcemia is considered mild if calcium value is 10 to 12 mg/dL; moderate if 12 to 14 mg/dL, and hypercalcemic crisis if 14 to 16 mg/dL. Intact PTH levels have a critical role in the investigation of etiology of hypercalcemia. Low PTH levels are indicative of malignancy. In the absence of malignancy, other endocrinopathies (hyperthyroidism, acromegaly, surrenal insufficiency) should be questioned. If PTH value is normal or high, 24-hour urine analysis should be performed. A low value of 24-hour urine calcium reflects familial hypocalciuric hypercalcemia; if the value is high, primary or tertiary hyperparathyroidism should be investigated (10). The treatment of primary hyperparathyroidism is surgical. Alternatives to surgery include ultrasonographic laser ablation and percutaneous ablation. Both methods can be done when surgery is contraindicated. Ablation is performed by USG-guided percutaneous interstitial laser photo coagulation (ILP) that can detect the diseased parathyroid gland. Additionally, ethanol might be injected into parathyroid adenoma percutaneously or angiographically for ablation (10). As our patient had stage 4 breast carcinoma (bone metastasis) with a life expectancy of nearly two years, ethanol injection was planned. But since the patient refused, surgery was performed. In conclusion, the involvement of PHPT in malignancy cases should be considered. Therefore, patients with malignancy and hypercalcemia, even if there is a bone metastasis, should be evaluated for PTH to exclude PHPT.

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