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SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

Hypoparathyroidism: A Rare Manifestation of Metastatic Breast Carcinoma

CASE REPORT
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ABSTRACT

Hypocalcemia is a disorder that may develop in cancer patients as a result of chemotherapeutic agents or tumor lysis syndrome. In rare situations, hypocalcemia may be due to hypoparathyroidism associated with bone-metastatic malignancy. Here, we report a 54-year-old woman with a known case of breast cancer, who presented to the hospital with numbness and paresthesia of the distal extremities 1 year after mastectomy and chemotherapy. She had low plasma calcium and parathyroid hormone levels, as well as a high serum phosphate level. Finally, she was treated with calcium gluconate infusion and calcitriol with a diagnosis of primary hypoparathyroidism. Overall, this case emphasizes the importance of measuring serum calcium levels in patients with metastatic bone carcinoma since this could affect their symptoms. Moreover, we should consider the probability of hypoparathyroidism in the differential diagnosis of hypocalcemic symptoms, even in patients with known malignancy.

Keywords: Hypocalcemia, breast neoplasm, hypoparathyroidism, bone metastasis, case report

Introduction

Hypercalcemia is one of the most common paraneoplastic syndromes in patients with cancer such as lung, breast, and hematological malignancy, which often indicates poor prognosis and advanced disease.[1] Secondary hyperparathyroidism may occur as a result of osteoblastic bone metastases or acute mineralization after tumor lysis syndrome. In contrast, hypocalcemia is an uncommon complication of malignant tumors.[2]

Hypocalcemia has been identified in 3 different types of cancer patients:[3] (i) the first group consists of patients with hematologic malignancies who experience severe hyperphosphatemia after treatment with cytolytic drugs, resulting in hypocalcemia, (ii) the second group consists of patients with solid tumors who develop hypocalcemia as a result of extensive osteoblastic metastases, and (iii) as a result of parathyroid gland involvement during disseminated metastatic tumors.[4]

There may be several factors involved in the development of hypocalcemia in patients with cancer, such as osteoblastic bone metastasis, hypomagnesemia, infiltrative and surgical hypoparathyroidism, hypoalbuminemia, vitamin D deficiency, sepsis, and side effect of drugs.[5]

Osteoblastic bone metastases are more common in patients with breast, prostate, or lung cancer.[3] Among these malignancies, hypocalcemia is more common in patients with prostate cancer than in those with breast cancer. Also, hypocalcemia is more commonly associated with low parathyroid hormone (PTH) levels.[6,7] Here, we report a 54-year-old woman with bone-metastatic breast cancer who developed severe hypocalcemia and hypoparathyroidism.

Case Report

A 54-year-old woman presented to the Endocrinology Department of Ghaem Hospital (Mashhad, Iran) with a 1-month history of numbness and paresthesia of the distal extremities. First, she was treated with calcium and vitamin D replacement, but because of recurrent hypocalcemic symptoms, she was referred for endocrine workup. In her past medical history, she had been diagnosed with right breast carcinoma for 2 years, undergoing a mastectomy followed by radiotherapy and chemotherapy (doxorubicin, cyclophosphamide, trastuzumab, vinorelbine, and exemestane). Moreover, 5 months before admission, thoracolumbar metastases (T11, T12, L4, and L5 vertebrae) were detected in a whole-body bone scan (Figure 1).

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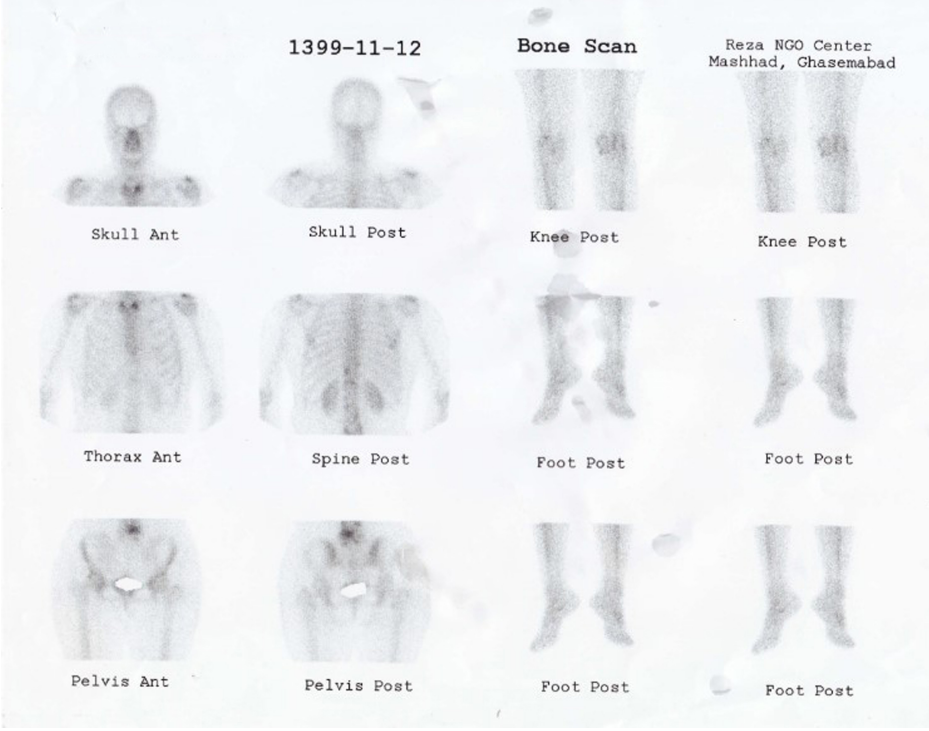

Figure 1. Bone scan of the patient revealing extensive generalized skeletal uptake.

One year after chemotherapy and radiotherapy, she developed hypocalcemic symptoms.

On physical examination, she had a systolic/diastolic blood pressure of 108/80 mmHg, a heart rate of 82 beats/min, and a respiratory rate of 18 breaths/min. Thyroid examination revealed both lobes of the thyroid gland palpable and nodular. The Chvostek and Trousseau's signs were negative because she was on replacement therapy with calcium and vitamin D.

In the initial laboratory studies, complete blood count and thyroid hormone levels were normal. The serum calcium level was 6.4 mg/dL (reference range, 8.5-10.5 mg/dL), phosphorus 8.7 mg/dL (reference range, 2.5-4.5 mg/dL), creatinine was 0.8 mg/dL (reference range, 0.7-1.3 mg/dL), albumin 4.3 g/dL (reference range, 3.5-5 g/dL), 25-hydroxyvitamin D (25(OH) D) 25 ng/mL (reference range, 20-40 ng/mL), magnesium (Mg) 2.5 mg/dL (reference range, 1.7-2.4 mg/dL), alkaline phosphatase 220 IU/L (reference range, 44-147 IU/L), and PTH level was 5.95 pg/mL (reference range, 12-65 pg/mL).

Hypocalcemia and reduced PTH were confirmed in the repeated investigation. Calcium range was 6.4-7.2 mg/dL, phosphorus range was 5.2-8.7mg/dL, and PTH range was 5.5-5.95 pg/mL.

MAIN POINTS

- Hypocalcemia can be a complication of bone metastatic breast cancer.
- Hypoparathyroidism may be the late presentation of breast cancer associated paraneoplastic syndrome.
- Hypoparathyroidism could be the side effect of radiotherapy in breast cancer.
- Hypoparathyroidism may be the adverse effect of chemotherapy in breast cancer.

Common causes of hypocalcemia (renal failure, vitamin D deficiency, pancreatitis, malabsorption, and hypomagnesemia) were ruled out. Her family history was unremarkable, and she was a lifelong non-smoker.

Ultrasonography revealed 2 hyperechoic solid nodules (26 mm, 27 mm) in the left lobe of the thyroid gland with a benign appearance and the parathyroid area was without a mass lesion. The patient was treated with calcium gluconate infusion and calcitriol with a diagnosis of primary hypoparathyroidism and then discharged on replacement therapy with oral calcium and calcitriol and thiazide. Informed consent was obtained from the patient to publish her information.

Discussion

Hypocalcemia is an uncommon electrolyte disorder that affects patients with metastatic bone carcinoma. It is more often associated with breast and prostate cancers, but it is also seen with other types of malignancies such as gastric cancer.[8-10] For the first time, Pepper et al[11] in 1984 reported a patient with osteoblastic metastases of breast cancer who had hypocalcemia.

This study showed that patients with osteoblastic metastases had a higher rate of calcium deposition in their bones.[11]

The incidence of hypocalcemia in cancer patients is not precisely known. In the study of D'Erasmo et al.[12] 10.8% of hospitalized patients were found to be hypocalcemic and in Blomqvist's[13] study on 7625 cancer patients, the incidence of hypocalcemia was 1.6% (calcium levels adjusted for albumin amounts).

The possible causes of treatment-resistant hypocalcemia are hypomagnesemia, hypoalbuminemia, renal failure, autoimmune hypoparathyroidism, vitamin D deficiency, calcium-lowering drugs, like

denosumab and bisphosphonate, and malignancies with osteoblastic bone metastases such as breast and prostate cancers.[14]

Although the exact pathogenic mechanism of hypocalcemia associated with osteoblastic bone metastasis is still unclear, it is often presumed that this is due to the higher calcium deposition in bone.[2]

Gröber and Kisters[15] reported a high prevalence of vitamin D deficiency and an association between lower 25(OH) D serum levels and higher mortality in breast cancer.[15]

Santini et al[16] observed that 25(OH) D levels fell considerably in breast cancer patients on antitumor treatment with anthracyclines and taxanes so it can be assumed that almost all breast cancer patients have a vitamin D deficiency.

Hypocalcemia was reported during chemotherapy with mithramycin, actinomycin D, cisplatinum, methotrexate, busulfan, and bleomycin. Mithramycin and actinomycin D may be by inhibiting bone resorption. The hypocalcemic effect of cisplatinum is secondary to renal magnesium wasting and magnesium deficiency.[17]

Hypocalcemia is diagnosed based on the presence of symptoms, which must be confirmed by a laboratory examination. Total serum calcium concentrations should be corrected with albumin levels because serum calcium is partially bonded to proteins.[18] To create an appropriate differential diagnosis, total protein, serum albumin, vitamin D, phosphate, urinary calcium, plasma PTH, and liver, and renal function must be evaluated.[18]

Hypoparathyroidism is an endocrine condition in which PTH production decreases, leading to low serum calcium and elevated serum phosphorus. It may develop due to parathyroid or thyroid gland surgery, genetic or autoimmune causes, the most common cases occur after thyroidectomy.[2]

Cooksley et al[19] reported a case of osteoblastic metastatic carcinoma of the breast with associated hypoparathyroidism leading to seizures and severe hypocalcemia. She was found to have metastatic carcinoma of the breast associated with hypoparathyroidism, leading to refractory hypocalcemia. Parathyroid metastases are found in 12% of postmortems in patients dying of malignant disease, with the breast being the most common primary. It has been suggested that parathyroid metastases result in hypoparathyroidism when at least 70% of the total gland mass is replaced by tumor.

In the review literature, a syndrome that consists of a combination of hypocalcaemia, hypomagnesaemia, and hypoparathyroidism in patients receiving treatment for acute leukemia was reported in 9 patients. All of them had been taking doxorubicin (or daunorubicin) and cytarabine. These drugs may have contributed to the suppression of parathyroid secretion.[20]

Temporary hypoparathyroidism was reported by Grieve et al.[21] They described 3 cases with metastatic breast cancer who had hypercalcemia. After the correction of hypercalcemia, they were treated with a combination of vincristine, adriamycin, and cyclophosphamide and had an excellent response. But 2 months later, they developed hypocalcemic symptoms and laboratory findings revealed severe hypocalcaemia and undetectable PTH. Replacement therapy with calcium and calcitriol was done. Replacement therapy was discontinued 2 months later. Follow-up PTH and calcium were normal in 2 cases.[21]

Our patient had no previous history of thyroid surgery. Also, she had not been treated with bisphosphonates. Moreover, her laboratory studies, including albumin, magnesium, and 25-hydroxyvitamin D, were within normal ranges. Our patient initially had low PTH and remained low for a long time, so she had primary hypoparathyroidism.

She was treated with doxorubicin, cyclophosphamide, trastuzumab, vinorelbine, and exemestane 1 year ago as mentioned earlier, and 2 of these drugs may contribute to hypoparathyroidism.

On review of the literature, there is no report of hypoparathyroidism due to treatment with trastuzumab and exemestane.

No specific etiology was detected for hypoparathyroidism in this case. Maybe it was due to diffuse infiltration of the parathyroid gland or secondary to the toxic effect of chemotherapy or the side effect of radiation.

Hypocalcemia is treated differently based on its clinical presentation, severity, and underlying causes. The treatment goal in cases of hypocalcemia along with primary hypoparathyroidism is to minimize symptoms, ensure appropriate serum calcium levels, and low calcium-to-phosphate ratio to avoid hypercalciuria and calcium salt deposition in soft tissues.[22] Calcitriol, an analog of vitamin D, can be used for treatment, with a starting dosage of 0.5 μg/day and increased until sufficient serum calcium levels are reached.[18] Our patient was treated and discharged on replacement therapy with oral calcium, calcitriol, and thiazide. She has been visited every 6 months and continued replacement therapy.

Conclusion

Hypocalcemia is an unusual but known complication of breast cancer with bone metastases. Of note, we should consider hypoparathyroidism in the differential diagnosis of hypocalcemic symptoms as a paraneoplastic syndrome.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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