Liver-Directed Embolization for the Long-Term Control of Hypercalcemia of Malignancy in Metastatic Breast Cancer

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Summary: Hypercalcemia of malignancy is a common complication of certain types of cancers. No standard therapies exist for the treatment of hypercalcemia secondary to paraneoplastic syndromes that result in the long-term control of serum calcium levels. We report a case of metastatic breast cancer with parathyroid hormone–related protein associated with hypercalcemia of malignancy that was treated with transarterial embolization of the hepatic metastatic lesions.

Introduction

Hypercalcemia of malignancy is a common complication of multiple myeloma and breast, prostate, and lung cancers, and it is most often due to osteolytic metastatic osseous lesions.1 Hypercalcemia secondary to the ectopic secretion of parathyroid hormone (PTH)–related protein frequently occurs in squamous cell lung cancer but is rare in breast cancer.2 In general, treatment for hypercalcemia of malignancy is symptomatically focused and involves intravenous hydration and bisphosphonates (eg, zoledronic acid) that can provide temporary control of calcium levels.3

In this report, we describe the first case of poorly differentiated breast carcinoma metastatic to the lymph nodes and liver with paraneoplastic hypercalcemia that was treated with transarterial embolization of the hepatic metastatic lesions.

Case Report

A 67-year-old woman presented with a palpable right axillary mass. Biopsy was performed and showed poorly differentiated breast carcinoma with neuroendocrine differentiation. Axillary mass tissue was HR positive and ERBB2 (formerly HER2/neu) negative. Initial computed tomography (CT) for staging identified suspicious liver lesions, and findings on liver biopsy revealed poorly differentiated metastatic carcinoma with neuroendocrine differentiation.

She underwent 6 cycles of cyclophosphamide/adriamycin. She responded well and began long-term letrozole. Four years after her initial diagnosis, follow-up imaging studies demonstrated disease progression in the liver. She was treated with 3 cycles of carboplatin/paclitaxel, but she had a minimal response.

Because of the liver-predominant disease, which did not respond to chemotherapy, the patient was referred for transarterial liver-directed therapy (Fig 1). She underwent radioembolization treatment with Y90 glass microspheres to the right and left lobes of the liver followed by capecitabine.

Eight months after radioembolization, she presented with complaints of lethargy and generalized weakness. Serial laboratory studies were obtained, the findings of which demonstrated progressive hypercalcemia with serum calcium levels between 12 and 16 mg/dL (normal range, 8.9–10.1 mg/dL). She received treatment...
on multiple visits with intravenous fluids and bisphosphonates, but she experienced only temporary improvement.

Further evaluation showed an elevated PTH-related protein level with a low intact PTH level of 15.1 pg/mL (normal range, 7.5–53.5 pg/mL). Follow-up CT demonstrated multiple subcentimeter-enhancing nodules in both lobes of the liver consistent with metastatic disease progression (Fig 2). The metastatic disease was confined to the liver and right axillary lymph nodes, and evidence of osseous metastasis was absent. Therefore, repeat transarterial liver-directed therapy was recommended to control the liver disease.

The patient underwent 2 interventions of transarterial bland embolization of the right hepatic lobe and treatment of the left hepatic lobe using 100 μm embolization microspheres within a 6-month period. Her serum calcium level decreased to 10.6 mg/dL after the first 2 interventions and to 9.8 mg/dL after embolization of the left lobe. Serum calcium was monitored at subsequent clinic visits, and her level remained in the normal range without additional interventions (lowest level, 8.7 mg/dL).

No complications or adverse events were observed. Her hypercalcemia was adequately controlled, and she did not require additional hospitalizations so she was able to continue on chemotherapy with exemestane and everolimus. CT obtained 21 months after the first bland embolization treatment demonstrated multiple, tiny calcified nodules in the liver that represented dystrophic calcifications of necrotic tumor nodules (Fig 3). No enhancing lesion in the liver was observed, indicating a complete radiographic response to embolization and subsequent chemotherapy.

**Discussion**

Hypercalcemia of malignancy affects 40% of patients, and it most commonly occurs in the advanced stages of malignancy. Four distinct causes of hypercalcemia have been described: (1) osteolytic hypercalcemia accounts for almost 20% of cases; (2) humoral hypercalcemia due to PTH-related protein accounts for nearly 80% of cases; and (3) 1,25(OH)–secreting lymphomas and (4) ectopic hyperparathyroidism account for approximately 2% of remaining cases. In metastatic breast cancer, hypercalcemia is most commonly caused by osteolytic lesions; however, secretion of PTH-related protein has been shown to be associated with local bone resorption in patients with metastatic breast cancer, even in the setting of a normal serum PTH-related protein level.

Regardless of the etiology, no standard therapy exists for the treatment of hypercalcemia of malignancy that results in the long-term control of serum calcium levels. Case reports have been published on the control of paraneoplastic hypercalcemia with transcatheter arterial chemoembolization in patients with hepatocellular carcinoma (HCC) and colorectal cancer metastatic to the liver without bone metastasis or increase in serum PTH-related protein level. Liver-directed transarterial embolization has been established as the primary therapy for hypercalcemia of malignancy related to humoral mediators secreted by HCC. Despite evidence of effective treatment of metastatic HCC using direct embolization, the evidence is scarce in metastatic breast cancer. In our case patient, hypercalcemia was due to an elevated level of PTH-related protein.
Conclusions
This report describes the first case of refractory hypercalcaemia secondary to a paraneoplastic syndrome in a patient with metastatic breast cancer to the liver that was treated with transarterial embolization. Hypercalcaemia most commonly occurs in the advanced stages of malignancy due to several factors. Most commonly, hypercalcaemia is due to excess secretion of PTH-related protein from tumor cells. In metastatic breast cancer, hypercalcaemia is most commonly due to osteolytic lesions. Regardless of etiology, only temporary control of hypercalcaemia is achieved.

References