CLINICAL VIGNETTE

Hypercalcemia in Malignancy

Grace I. Chen, MD and Erin A. Cook, MD

Case

An 82-year-old-female presented for an urgent visit after staff at her assisted living facility reported that she was acting differently and appeared weaker, with difficulty walking for one day. During the visit, she reported weakness in her arms and legs for the prior week. She now needed to use a walker or the assistance of another person to ambulate compared to independent ambulation baseline. She also reported right upper quadrant pain with inspiration over the past few days. Exam was only significant for a mild resting tremor, which was chronic and generalized weakness. There were no other focal findings, including negative Murphy's sign and no focal neurological deficits. Laboratory testing returned showing sodium 134 mEq/L, calcium (Ca) 11.9 mg/dL (reference range: 8.6-10.4 mg/dL), albumin 4.0 g/dL, alanine transaminase 78 U/L, aspartame aminotransferase 83 U/L and alkaline phosphatase 268 U/L (reference range: 37-113 U/L). The patient was directed to the Emergency Department (ED) for further evaluation given the lab abnormalities. In the ED, abdominal ultrasound showed numerous hepatic lesions. Computerized tomography (CT) scan of abdomen and pelvis showed innumerable liver metastases, scattered nodal metastases and mild peritoneal carcinomatosis. CT angiogram of the chest showed acute and subacute pulmonary venous thromboemboli in both lungs. A 3 centimeter peripherally enhancing mass was also seen on the right breast on both CTs. Lower extremity venous duplex showed acute deep venous thrombosis in the right femoral vein at the level of the mid-thigh and she was admitted for further evaluation and treatment.

The patient's past medical history include asthma, allergic rhinitis, hypertension, bipolar disease type II, dyslipidemia, prediabetes, obstructive sleep apnea, osteoporosis, osteoarthritis and constipation. She had last seen her primary care physician two months prior and her psychiatrist one month prior and no acute issues were noted at either visit. Her last calcium level was normal nine months prior, as was the last transaminase levels, sixteen months prior to presentation. Her last mammogram was also normal three years prior at age 79.

During the hospitalization, she received intravenous fluids, furosemide and a bisphosphonate to treat her hypercalcemia. Admission labs showed parathyroid hormone (PTH) 9 pg/mL (11-51 pg/mL), ionized calcium 1.52 mmol/L (1.09-1.29 mmol/L), parathyroid hormone-related peptide (PTHrP) 26 pmol/L (0.0-3.4 pmol/L) and 1,25-dihydroxy-vitamin D ($1,25(OH)_2$-vitamin D) 52.7 pg/mL (19.9-79.3 pg/mL). Magnetic resonance imaging (MRI) of her cervical, thoracic and lumbar spine showed degenerative disc disease, spinal spondylosis and severe lumbar stenosis, but no mass or abnormal enhancement. Clinically, her right upper quadrant pain improved with anticoagulation treatment of the pulmonary emboli and constipation. On hospital day 5, she underwent a percutaneous liver biopsy by interventional radiology. She was discharged home on hospital day 6 with scheduled follow up with oncology after breast MRI and a nuclear bone scan. Her hypercalcemia was hypothesized to be related to bony metastatic disease from presumed right breast cancer.

Nuclear bone scan was completed seven days after hospital discharge, and showed no evidence of metastatic bone disease. Patient had a post-hospital video visit with her primary care physician 15 days after hospital discharge. She reported feeling weaker, similar to when she presented to the hospital. She remained ambivalent about next steps of her care between seeking further evaluation and treatment versus pursuing a more comfort-focused approach. Three days after the video visit, the patient's sister reported that the patient had declined further and was much weaker. The following day, the patient's coronavirus disease 2019 (COVID-19) polymerase chain reaction (PCR) test returned positive and a repeat calcium level was 13.5 mg/dL. Based on these new developments, the patient's family opted to transition the patient to hospice and she died at home 12 days after hospice enrollment, 32 days after hospital discharge. On the day of her death, the pathology report from her liver biopsy returned showing "possibility of metastatic mammary adenoid cystic carcinoma."

Discussion

Adenoid cystic carcinoma (ACC) of the breast is a rare special subtype of breast cancer that displays a triple-negative phenotype, but is usually low-grade and exhibits an indolent clinical behavior unlike most triple-negative breast cancers which are generally high-grade tumors with an aggressive clinical course.[1] Triple-negative breast cancer is characterized by lack of expression to estrogen and progesterone receptors and the absence of HER2 protein overexpression.[2] Lack of these characteristics in triple-negative breast cancer limits tumor-specific endocrine treatment options. Although this patient had a rare triple-negative breast cancer subtype with a typically indolent course, she unfortunately already had advanced

disease by the time of diagnosis, with hypercalcemia further predicting a poor prognosis.

Hypercalcemia, which occurs in up to 30% of patients with a malignancy, typically is a manifestation of later stages of malignancy and predicts a poor prognosis.[3] Common causes include humoral hypercalcemia of malignancy mediated by increased PTHrP, local osteolytic hypercalcemia with secretion of other humoral factors responsible for hypercalcemia, excess $1,25(OH)_2$-vitamin D production, concurrent hyperparathyroidism and multiple other concurrent etiologies. Hypercalcemia is four times more common in stage IV malignancies and most common in lung cancer, multiple myeloma, and renal cell carcinoma,[4] followed by breast cancer and colorectal cancer. One retrospective study, reports median survival of 30 days.[5]

Humoral hypercalcemia from PTHrP-mediated hypercalcemia causes 80% of hypercalcemia in cancer patients. This is more common than hypercalcemia related to metastatic disease to the bone and was the cause in this patient. PTHrP is structurally similar to PTH, so it can mimic the bone and renal effects of PTH. It enhances renal tubular re-absorption of calcium while simultaneously increasing urinary phosphorus excretion. This process results in hypercalcemia and hypophosphatemia but does not increase $1,25(OH)_2$-viamin D and so does not increase skeletal tumor burden. PTHrP acts on osteoblasts and increases synthesis of receptor activator of nuclear factor kappa-B ligand (RANKL).[6]

Current treatment of hypercalcemia is based on the patient's symptoms and absolute serum calcium level and not on etiology. Treatment goal is to lower serum calcium concentration by inhibiting bone resorption, usually through bisphosphonates, and increasing urinary calcium excretion, generally with aggressive hydration. Denosumab, a monocolonal antibody against RANKL, has been used with some success in cases refractory to bisphosphonates. In the future, patients with humoral hypercalcemia from PTHrP-mediated hypercalcemia, may be treated with an anti-PTHrP antibody which appear promising in murine animal models.[7-8]

The recurrence and worsening hypercalcemia in this patient indicated further progression of malignancy with ongoing humoral secretion from PTHrP. The role of the COVID-19 infection in her death is not clear, but was unlikely to have significantly altered the trajectory given her advanced malignancy.

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