CLINICAL VIGNETTE

Hypercalcemia in a Patient with Pancreatic Adenosquamous Carcinoma: A Serious Complication from a Rare Cancer

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Introduction

Hypercalcemia of malignancy is a well-known complication of cancer, most commonly seen with advanced breast, renal, and lung cancer, as well as multiple myeloma.[1] We present a patient with acute hypercalcemia secondary to rare pancreatic adenosquamous carcinoma.

Case

A 41-year-old male with no known medical history initially presented to the emergency department complaining of loose stools and abdominal pain. CT abdomen showed a 6.4cm infiltrating pancreatic tail mass invading the stomach, spleen, and colon, in addition to liver metastases. Liver biopsy was consistent with pancreatic adenosquamous carcinoma. CA 19-9 was elevated to 129 units/mL (reference range <35 units/mL) and CEA was 7.8ng/mL (reference range 5.1-10ng/mL).

The patient was started on first-line chemotherapy with mFOLFIRINOX (oxaliplatin, leucovorin, irinotecan, fluorouracil). After completing five cycles of chemotherapy, restaging CT showed progressive disease with CA 19-9 elevation to 1343 units/mL. The patient was planned to be transitioned to 2nd line chemotherapy with gemcitabine and abraxane.

One week after the CT was completed, the patient returned to the emergency department complaining of worsening fatigue, weakness, and vomiting for five days. Physical exam was remarkable for diffuse hyperreflexia, with 4+ patellar, biceps, and triceps reflexes. Labs were notable for hypercalcemia of 14.1mg/dL (15.2mg/dL when corrected for albumin), in contrast to a normal calcium level of 9.7mg/dL (reference range 8.9-10.3mg/dL) one week prior. The patient was started on intravenous normal saline, calcitonin, and zolendronic acid. His hypercalcemia rapidly improved, and calcium level had decreased to 9.6mg/dL two days after admission. His symptoms and hyperreflexia resolved, following normalization of his calcium levels.

Labs drawn during admission revealed elevated parathyroid hormone-related protein (PTHrP) of 39pg/mL (reference range 11-20pg/mL). PTHrP had been normal at 17pg/mL two months prior. Other labs showed decreased PTH of 3pg/mL (reference range 15-65pg/mL), normal Vitamin D 25-OH level of 34ng/mL (30-100ng/mL), and normal Vitamin D 1,25-OH level of 61pg/mL (reference range 18-64pg/mL).

Discussion

Hypercalcemia of malignancy is a well-known complication of cancer. The prevalence has been reported to affect 2% to 44% of cancer patients.[1,2] This complication is most commonly seen with late-stage breast, renal, and lung cancer, as well as multiple myeloma.[2]

There are four major mechanisms that can lead to hypercalcemia in malignancy. The first is the production of PTHrP by cancer, also called humoral hypercalcemia of malignancy. PTHrP acts on the same receptors as parathyroid hormone (PTH). Overproduction of PTHrp is most commonly seen in squamous cell carcinomas. The second is ectopic production of PTH, which is most commonly seen in parathyroid cancers. The third is over-activation of the conversion of inactive 25-hydroxyvitamin D into the active form of 1,25-dihydroxy-vitamin D. These three mechanisms lead to elevation in calcium concentrations by increasing the activation of Vitamin D, increasing calcium reabsorption by the kidney, and increasing breakdown of bone. The fourth mechanism is the direct breakdown of bone via a malignant osteolytic lesion, causing release of calcium into the bloodstream.[1]

Pancreatic adenosquamous is a rare and aggressive malignancy, estimated to comprise 0.38%-10% of all pancreatic cancers.[3] As opposed to the majority of pancreatic cancers which are adenocarcinomas, this form of malignancy shows mixed adeno-carcinoma and squamous carcinoma. This is hypothesized to originate from squamous metaplastic changes from pancreatic adenocarcinoma. Tumor cell necrosis, high tumor grade, and poor differentiation are commonly seen.[3,4] These factors lead to

poor prognosis with median survival of less than 6 months and overall 2-year survival of 11%.[4] Hypercalcemia is not typically associated with the more common histologic subtype, pancreatic adenocarcinoma. However, pancreatic adenosquamous carcinoma represents a unique entity that may be more prone to hypercalcemia due to its squamous cell component.

We hypothesize that this patient's hypercalcemia was due to PTHrP production by his pancreatic adenosquamous carcinoma. A literature search for other cases of hypercalcemia in patients with pancreatic adenosquamous carcinoma shows that PTHrP was also found to be elevated in those cases. Immunohistochemistry staining showed PTHrP localization in cancer cells.[5-7]

In conclusion, it is important to monitor for hypercalcemia in patients with pancreatic adenosquamous carcinoma. Increased clinical suspicion is warranted particularly in symptomatic patients with known progressive disease, as hypercalcemia can be an early sign of rapidly progressive disease. Awareness can lead to early detection and avoidance of serious complications secondary to severe hypercalcemia.

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