Metastatic Calcification of Multiple Visceral Organs in Non-Hodgkin's Lymphoma

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A patient with non-Hodgkin's lymphoma who developed acute hypercalcemia following chemotherapy was evaluated for skeletal metastases with a whole-body bone scan. Although metastatic disease is an unlikely cause of hypercalcemia, considering the acutely rising serum calcium, the bone scan is useful in excluding multiple metastases as a cause. In addition, the study demonstrated metastatic calcification in multiple organs, including the pancreas which is uncommon, and the liver and spleen, which is rare.

Key Words: lymphoma; hypercalcemia; chemotherapy; metastatic calcification

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Metastatic calcification of soft tissues is a known complication of various pathologies. Bone scanning with ^{99m}Tc-diphosphonate compounds often reveals extraosseous pathologies, including dystrophic or metastatic calcification. A bone scan has also been reported to be more sensitive than plain radiography or CT in detecting metastatic calcification (*1–3*). This case is unusual in that metastatic calcification of the liver and spleen is uncommon and metastatic calcification in the pancreas is rare (*4*).

CASE REPORT

A 64-yr-old man developed a left chest wall mass in April 1993 and was found to have non-Hodgkin's lymphoma. He was treated with six courses of chemotherapy and had complete remission by October 1993. In December 1993, he had a recurrence of the chest wall mass and developed a malignant left pleural effusion. He received radiotherapy and was admitted for repeat chemotherapy. On admission, the patient was hypokalemic (potassium 3 mEq/liter, normal range: 3.5–5.0 mEq/liter) with low normal serum calcium (8.8 mg/dl, normal range: 8.5–11.0 mg/dl), borderline low albumin (3.4 g/dl, normal range 3.5–4.9 g/dl) and high normal serum phosphorus (4.5 mg/dl, normal range: 2.4–4.7 mg/dl). BUN and serum creatinine were normal. The patient was treated with chemotherapy and developed lethargy, confusion, disorientation and weight loss several days later. He was found to have hypercalcemia and hyperphosphatemia (total calcium 14.3 mg/dl, phosphorus 7.1 mg/dl, albumin 2.6 g/dl). The intact parathyroid hormone was 11 pg/ml (normal 10–68 pg/ml).

A bone scan was ordered at that time to exclude osseous metastases. Planar imaging was performed 3 hr after injection of 24 mCi of ^{99m}Tc-methylene diphosphonate (MDP) and showed normal distribution of radiotracer in the skeleton. Both planar (Fig. 1) and SPECT imaging (Fig. 2) showed extensive visceral activity in both lungs, the heart, liver, spleen, pancreas, kidneys and stomach. Thin-layer chromatography of the reconstituted ^{99m}Tc-MDP kit showed less than 3% of free pertechnetate. Furthermore, bone scans of other patients injected with the same kit showed no evidence of radiopharmaceutical impurity. A chest x-ray obtained at that time showed a left pleural effusion and several infiltrates in the lungs but no evidence of soft-tissue calcification. A CT scan of the abdomen detected several small calcifications at the dome of the liver, but was otherwise normal. The hypercalcemia was treated with hydration, furosemide calcitonin and pamidronate disodium with prompt response. The calcium level fell to 9.5 mg % and the phosphorus to 4.2 mg % within 1 wk. Renal function, however, did not improve significantly, and the patient died 1 wk later.

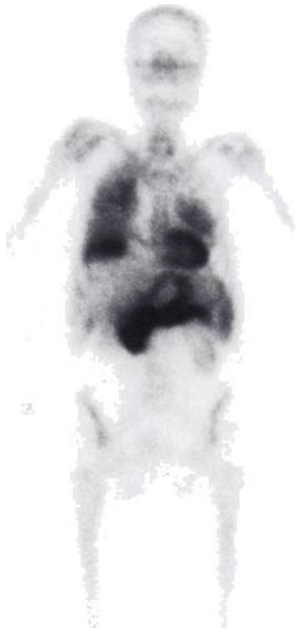

FIGURE 1. Anterior planar view of the whole body shows normal distribution of ^{99m}Tc-MDP in the skeleton as well as prominent soft-tissue activity in multiple visceral organs of the chest and abdomen.

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FIGURE 2. Representative transaxial SPECT slices of the abdomen demonstrate clear uptake in the head of the pancreas (large arrow), body of pancreas (double arrows) and spleen (small arrow).

DISCUSSION

Metastatic calcification is often associated with chronic renal failure, secondary hyperparathyroidism (*5–6*) and malignant diseases (*1,2,4*). Primary hyperparathyroidism (*1,7*) and hypervitaminosis D are less common causes. Whereas metastatic calcification occurring in the absence of hypercalcemia is mainly associated with chronic renal failure (*8*), it is usually accompanied by hypercalcemia in other patients. Extensive destruction of bone by skeletal metastases is a known cause of hypercalcemia (*3*). Other distinct mechanisms of hypercalcemia were also recognized in patients with malignant disease: ectopic production of parathyroid hormone-like substances by tumors or osteoclast-stimulating factors such as interleukin 1 and prostaglandins (*2,9*). More recent evidence suggests that local or systemic humoral mediators released by a tumor may be responsible for bone destruction and subsequent hypercalcemia (*10–11*).

Acute hypercalcemia which immediately followed chemotherapy in this patient is unusual. The lysis of the lymphoma presumably led to the release of an osteoclast-stimulating cytokine, which caused the release of calcium from bone and hypercalcemia (*12–13*). Although underlying disease and calcium and phosphate levels may vary from patient to patient, the increase in the ion-product of calcium and phosphate appears to be an important factor in the precipitation of these substances in the soft tissues (*6*). A [Ca] × [P] product of 58–60 is considered the saturation point of normal serum above which spontaneous precipitation may occur (*14*). In hypercalcemic patients, the initial visceral deposit has been shown to be brushite ($CaHPO_4 \cdot 2H_2O$), which is subsequently transformed to apatite [$Ca_{10}(PO_4)_6 \cdot (OH)_2$] (*15*). Technetium-99m-labeled phosphate or diphosphonate compounds are known to bind to hydroxyapatite crystals, probably by chemisorption (*16*).

Calcium has a predilection for depositing in the kidneys, lungs and stomach. A higher pH in the extracellular fluid of these organs was proposed as a contributing factor (*2,17*). In our patient with non-Hodgkin's lymphoma and hypercalcemia, calcification was also present in multiple other organs, which may be related in part to the high ion-product of calcium and phosphate. Although metastatic disease was an unlikely cause of hypercalcemia because serum calcium increased acutely, the bone scan was clearly useful in excluding multiple metastases as a cause.

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