A Reversible Gastric Uptake of Bone Scintigraphy in a Patient with Hypercalcemia

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Abstract:
Hypercalcemia is a severe complication in cases of vitamin D intoxication that can result in metastatic calcification. We herein report a female case with hypercalcemia due to eldecalcitol administration associated with the increased uptake of technetium-99m hydroxymethylene diphosphonate (⁹⁹mTc-HMDP) as the bone-scanning agent in the stomach. A histologic assessment using biopsy specimens identified metastatic calcification of the stomach. After the normalization of serum calcium levels, the gastric uptake of ⁹⁹mTc-HMDP disappeared. This case indicates the usefulness of bone scintigraphy with ⁹⁹mTc-HMDP to detect visceral metastatic calcification and to monitor its therapeutic effects in patients with hypercalcemia.

Key words: bone scintigraphy, hypercalcemia, kidney disease, metastatic calcification, vitamin D

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Introduction
Pathological tissue calcification is mainly classified into two types: dystrophic calcification and metastatic calcification (1). Dystrophic calcification occurs after tissue injury in the presence of normal calcium and phosphate concentrations. In contrast, metastatic calcification is calcium deposits within extra-skeletal tissues due to abnormal calcium and phosphate metabolism (1). The etiology of metastatic calcification includes multiple myeloma, malignant lymphoma, breast cancer, hyperparathyroidism, vitamin D intoxication and chronic kidney disease (2). In both malignant and non-malignant conditions, an impaired renal function is a prerequisite for the development of metastatic calcification (3).

In this manuscript, we report a case of metastatic calcification in the stomach caused by hypercalcemia. Bone scintigraphy with technetium-99m hydroxymethylene diphosphonate (⁹⁹mTc-HMDP) showed an extensive uptake in the stomach, and a histologic assessment using biopsy specimens identified it as metastatic calcification. After the normalization of the serum calcium levels, the gastric uptake of ⁹⁹mTc-HMDP disappeared. Therefore, our case indicates the usefulness of bone scintigraphy to detect visceral metastatic calcification and monitor its therapeutic effects in patients with hypercalcemia.

Case Report
A 46-year-old woman was admitted to our hospital due to a 3-month history of anorexia and worsening renal function. She also presented with mild thirst on admission. She had been diagnosed with chronic kidney disease (CKD) G4A1 due to unknown origin since her 30s but had no history of diabetes mellitus or ischemic heart disease. She had also been treated for osteoporosis since 12 months before admission and had been taking oral eldecalcitol (0.75 μg/day) and intravenous alendronate sodium hydrate (900 μg/4 weeks). Neither thiazides nor any other medications affecting calcium metabolism had been prescribed before admission. The baseline level of serum corrected calcium was 9.2 mg/dL before the treatment for osteoporosis.

A physical examination on admission revealed a height of 153 cm, body mass index of 12.1 kg/m², body temperature of 37.2°C, pulse rate of 84 beats/min and blood pressure of 82/56 mmHg.

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In these cases, Corstens et al. (9) first reported that the gas-
blast growth factor-23 (FGF-23) level and the ionized cal-
cium level were high at 36,600 pg/mL (normal range: 10-
50) and 3.54 mEq/L (normal range: 2.41-2.72), respectively.
In addition, the serum bone alkaline phosphatase (BAP)
level and the serum tartrate-resistant acid phosphatase-5b
(TRACP-5b) level were 12.2 μg/L (normal range: 3.8-22.6)
and 70 mU/dL (normal range: 120-420), respectively.

Based on the combination of an impaired renal function
with a relatively low PTH level and a history of taking elde-
calcitol, she was diagnosed with hypercalcemia caused by
vitamin D analogue intoxication.

Computed tomography (CT) of the chest and abdomen re-
vealed bilateral nephrocalcinosis, although there was no evi-
dent calcification in other organs, such as the stomach or
lungs (Fig. 1). To identify pathologic calcification caused by
hypercalcemia, we performed bone scintigraphy with 99mTc-
HMDP, which showed a remarkable uptake in the upper part
of the stomach and slight uptake in the bilateral kidneys
(Fig. 2A). Next, we performed upper gastrointestinal endo-
scopy, and the mucosa of the stomach showed mild gastritis
without malignancy. Von Kossa staining of the biopsy spec-
imen in the stomach revealed calcium deposition in the inter-
glandular tissues of the fundus and the body but not the py-
lorus. These histologic findings were considered consistent
with metastatic calcification of the stomach (Fig. 3).

After admission, the patient was immediately treated with
intravenous saline administration, and eldecalcitol was dis-
continued. The serum corrected calcium levels decreased
and became normalized from 14.3 mg/dL to 8.7 mg/dL on
the 12th day, and the serum creatinine levels also decreased
from 2.43 mg/dL to 1.77 mg/dL on the 22nd day. After the
normalization of the serum calcium levels, her symptoms
improved, and the gastric uptake of 99mTc-HMDP disap-
ppeared (Fig. 2B).

**Discussion**

The interesting point of our case was the calcium deposi-
tion in the gastric mucosa, which was found by bone scin-
tigraphy and confirmed by a histological examination. De-
tection of visceral metastatic calcification by bone scintigra-
phy with 99mTc-phosphate complexes has often been reported
in cases of hypercalcemia (3, 4). However, there are few
cases in which metastatic calcification was proven histologi-
cally, and most were autopsy cases without any follow-up of
their clinical course (3, 5, 6).

Thus far, there have been five reported cases of visceral
metastatic calcification that was visualized by bone scintig-
raphy and confirmed by a histological examination (6-10).
In these cases, Corstens et al. (9) first reported that the gas-
tric uptake of 99mTc-phosphate complexes was reversed after
the improvement of hypercalcemia. Accordingly, our case is
the second case of metastatic calcification in the stomach to
be confirmed histologically and to be observed the reversi-
bility of the gastric uptake of the bone scan agent after the
are secreted, visceral metastatic calcification is observed and lungs are the three chief organs in the body where acids resulting in local alkalinity. Because the stomach, kidneys should produce the same amount of alkaline at the site, thus environment than in an acidic one. The secretion of acid absorption marker, was low, as eldecalcitol and alendronate also been reported in patients with an impaired renal func-

Elevated serum FGF-23 levels have sensing receptors, and hyperphosphatemia stimulates the secretion of PTH via calcium-
calcemia suppresses the secretion of PTH via calcium-

hypercalcemia, as it can lead to organ impairment (17). However, it is normally asymptomatic, and the radiographic detection of microscopic calcification is difficult. McLaugh-

metastatic calcification is an important complication in hypercalcemia, as it can lead to organ impairment (17). However, it is normally asymptomatic, and the radiographic detection of microscopic calcification is difficult. McLaugh-

Figure 2. The planar images (upper panels) and the fused single-photon emission computed tomographic (SPECT) and computed tomographic (CT) images (lower panels) from bone scintigraphy with technetium-99m hydroxymethylene diphosphonate ($^{99m}$Tc-HMDP). (A) The planar and fused SPECT/CT images revealed an extensive uptake in the upper part of stomach (arrowheads) and slight uptake in the bilateral kidneys before the improvement of hypercalcemia (Before). (B) After the normalization of the serum calcium levels, the gastric uptake of $^{99m}$Tc-HMDP disappeared (After). CT: computed tomography, SPECT: single-photon emission computed tomography, $^{99m}$Tc-HMDP: technetium-99m hydroxymethylene diphosphonate

Figure 3. (A) Hematoxylin and Eosin staining of the biopsy specimen in the stomach (magnification, ×40). (B, C) Von Kossa staining revealed the calcium deposition in the interglan-
dular tissues of the fundus and body (arrowheads) but not the pylorus [magnifications, (B) ×40 and (C) ×200].

treatment of hypercalcemia.

The present patient was diagnosed with hypercalcemia caused by eldecalcitol administration for the treatment of osteoporosis. Active vitamin D and vitamin D analogues, including eldecalcitol, stimulate the intestinal absorption of calcium and phosphate, although patients with an impaired renal function have a reduced ability to excrete excess calcium and phosphate (11). In fact, our case showed both hypercalcemia and hyperphosphatemia on admission. Hyper-
calcemia suppresses the secretion of PTH via calcium-sensing receptors, and hyperphosphatemia stimulates the secretion of FGF-23 (12). Elevated serum FGF-23 levels have also been reported in patients with an impaired renal function (13). In contrast, the serum level of TRACP-5b, a bone absorption marker, was low, as eldecalcitol and alendronate sodium hydrate suppress the bone absorption (14, 15). As a result, these findings including PTH, FGF-23, TRACP-5b or BAP were considered to indicate a diagnosis of hypercal-
cemia caused by eldecalcitol.

Calcium salts are more likely to precipitate in an alkaline environment than in an acidic one. The secretion of acid should produce the same amount of alkaline at the site, thus resulting in local alkalinity. Because the stomach, kidneys and lungs are the three chief organs in the body where acids are secreted, visceral metastatic calcification is observed mainly in these three organs (16). Furthermore, Gorospe et al. (1) showed that calcium deposits were limited to the interglan-
dular tissues of the fundus and the body in the stom-
ach (i.e., the location of the acid-secreting parietal cells), which was certainly consistent with the findings of our case.

Metastatic calcification is an important complication in hypercalcemia, as it can lead to organ impairment (17). However, it is normally asymptomatic, and the radiographic detection of microscopic calcification is difficult. McLaugh-
in et al. (18) reported that bone scintigraphy was the most sensitive imaging modality for detecting metastatic calcifica-
tion in patients with hypercalcemia. In fact, we were unable to detect gastric calcification by X-ray or CT, but the presence of microscopic calcification was suggested by bone scintigraphy and was confirmed by a histologic examination. Taken together, these findings suggest several strengths of
our case, as we were able to detect gastric calcification by bone scintigraphy and observe the reversibility of the gastric uptake of $^{99m}$Tc-phosphate complexes after the treatment of hypercalcemia.

However, the present case also has several limitations. First, the uptake of $^{99m}$Tc-phosphate complexes in the bone scintigraphy does not directly indicate the anatomic presence of calcification, although it reflects the increased activity of pathologic calcification. Second, the reason as to why the extensive uptake of $^{99m}$Tc-HMDP was limited in the stomach, but not in the lungs or the kidneys, remained unclear. The extensive uptake might be caused by tissue injury under the presence of gastritis in our case, although the further accumulation of cases is needed to identify the mechanism. Third, we were unable to distinguish whether anorexia had been caused by either hypercalcemia itself or metastatic calcification in the stomach.

In conclusion, the gastric uptake of $^{99m}$Tc-HMDP reversed after the improvement of hypercalcemia in a patient with eldecalcitol intoxication. We therefore propose that bone scintigraphy should be performed in hypercalcemic patients suspected of having metastatic calcification. Our case also suggests that eldecalcitol should be carefully administered in order to avoid unexpected hypercalcemia in patients with an impaired renal function.

The authors state that they have no Conflict of Interest (COI).

References


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