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【 CASE REPORT 】

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 (^{99m}Tc-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 ^{99m}Tc-HMDP disappeared. This case indicates the usefulness of bone scintigraphy with ^{99m}Tc-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 (^{99m}Tc-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 ^{99m}Tc-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/m^2, body temperature of 37.2℃, pulse rate of 84 beats/min and blood pressure of 82/56 mmHg.

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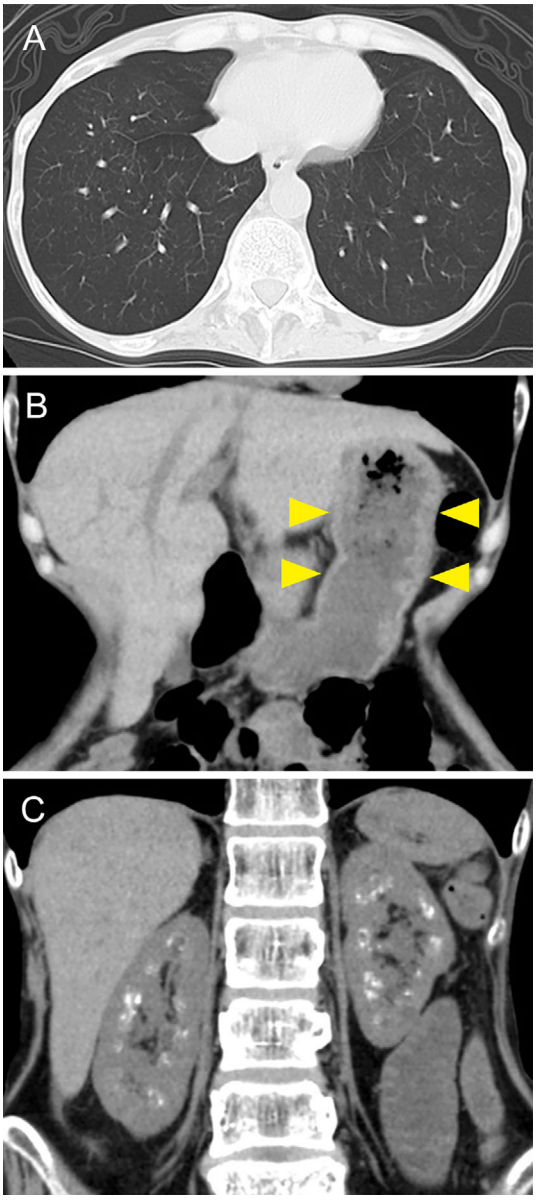

Figure 1. **(A) An axial image of a chest computed tomographic (CT) scan in the pulmonary window setting. No calcification was observed in the lung field. (B, C) The coronal reconstructed images of abdominal CT scans. No calcification was observed in the gastric wall of the fundus or the body (B, arrowheads). However, multiple calcium depositions were observed in the medullary regions of the bilateral kidneys (C). CT: computed tomography**

Laboratory studies on admission revealed a white blood cell count of 9,000/mm^3, hemoglobin of 8.6 g/dL, serum albumin of 2.5 g/dL, alkaline phosphatase of 282 U/L, blood urea nitrogen (BUN) of 20 mg/dL, serum creatinine of 2.43 mg/dL, estimated glomerular filtration rate (eGFR) of 18 mL/min/1.73 m^2, sodium of 139 mEq/L, potassium of 4.6 mEq/L, corrected calcium of 14.3 mg/dL, phosphate of 7.2 mg/dL, magnesium of 2.0 mg/dL, and C-reactive protein (CRP) of 0.38 mg/dL. The intact parathyroid hormone (PTH) level was relatively low at 13 pg/mL (normal range: 10-65), and the 1,25-dihydroxyvitamin D level was low at 13.7 pg/mL (normal range: 20.0-60.0), although the fibroblast growth factor-23 (FGF-23) level and the ionized calcium 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 eldecalcitol, she was diagnosed with hypercalcemia caused by vitamin D analogue intoxication.

Computed tomography (CT) of the chest and abdomen revealed bilateral nephrocalcinosis, although there was no evident calcification in other organs, such as the stomach or lungs (Fig. 1). To identify pathologic calcification caused by hypercalcemia, we performed bone scintigraphy with ^{99m}Tc-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 endoscopy, and the mucosa of the stomach showed mild gastritis without malignancy. Von Kossa staining of the biopsy specimen in the stomach revealed calcium deposition in the interglandular tissues of the fundus and the body but not the pylorus. 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 discontinued. 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 ^{99m}Tc-HMDP disappeared (Fig. 2B).

Discussion

The interesting point of our case was the calcium deposition in the gastric mucosa, which was found by bone scintigraphy and confirmed by a histological examination. Detection of visceral metastatic calcification by bone scintigraphy with ^{99m}Tc-phosphate complexes has often been reported in cases of hypercalcemia (3, 4). However, there are few cases in which metastatic calcification was proven histologically, 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 scintigraphy and confirmed by a histological examination (6-10). In these cases, Corstens et al. (9) first reported that the gastric uptake of ^{99m}Tc-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 reversibility of the gastric uptake of the bone scan agent after the

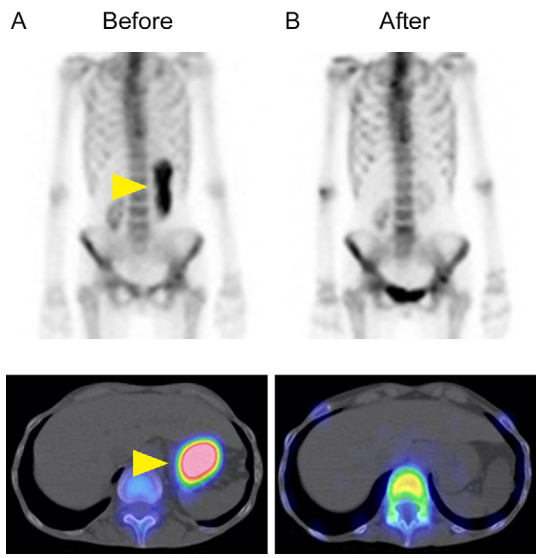

Figure 2. **The planar images (upper panels) and the fused single-photon emission computed tomographic (SPECT) and computed tomographic (CT) images (lower panels) from bone scintigraphy with technetium-99m hydroxymethylene diphosphonate (^{99m}Tc-HMDP). (A) The planar and fused SPECT/CT images revealed 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**

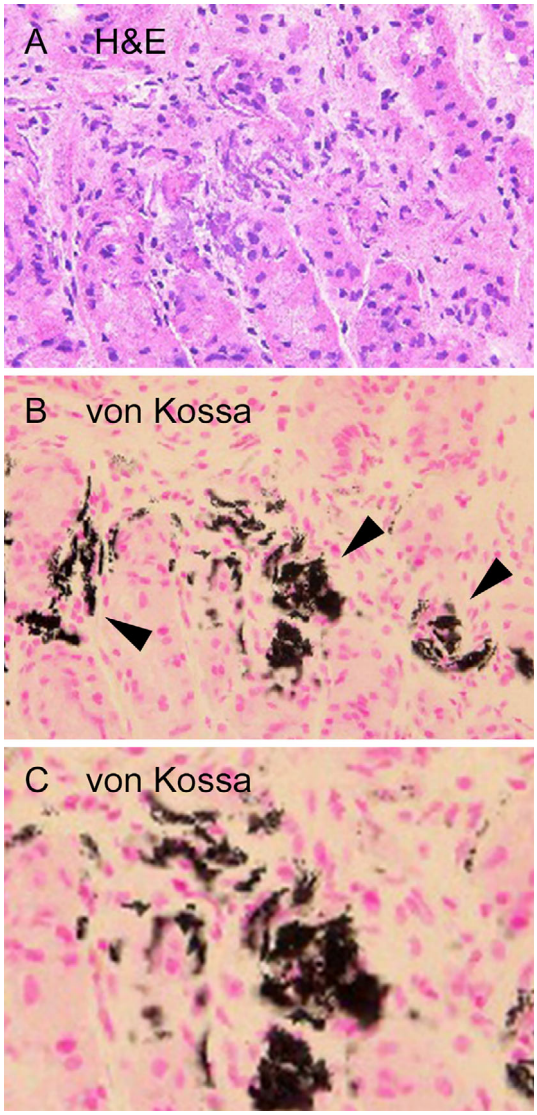

Figure 3. **(A) Hematoxylin and Eosin staining of the biopsy specimen in the stomach (magnification, ×40). (B, C) Von Kossa staining revealed the calcium deposition in the interglandular tissues of the fundus and body (arrowheads) but not the pylorus [magnifications, (B) ×40 and (C) ×200].**

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. Hypercalcemia 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 hypercalcemia 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 interglandular tissues of the fundus and the body in the stomach (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. McLaughlin et al. (18) reported that bone scintigraphy was the most sensitive imaging modality for detecting metastatic calcification 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).

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