Resolution of Massive Technetium-99m Methylene Diphosphonate Uptake in the Stomach in Vitamin D Intoxication

Frans Corstens, Adrian Kerremans, and Roland Claessens

Departments of Nuclear Medicine and Internal Medicine, St. Radboud University Hospital, Nijmegen, The Netherlands

Vitamin D intoxication, which may result from zealous intake of health food supplements, may cause metastatic calcification. This is the first reported case of a patient with vitamin D intoxication who had massive gastric uptake of [^{99m}Tc]MDP, but no lung uptake, with histologic documentation of the metastatic calcification by gastric biopsy. It is probable that the metastatic calcification was a highly metabolic process in this patient since the gastric uptake resolved within 3 wk when serum calcium and phosphate had returned to normal.

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Extraskeletal uptake of technetium-99m (^{99m}Tc) phosphate and phosphonate radiopharmaceuticals has been reported in a wide variety of conditions (*1*). Elevated stomach uptake of ^{99m}Tc methylene diphosphonate ([^{99m}Tc]MDP) is usually secondary to free pertechnetate (*2*). However, gastric uptake has been described in patients with hypercalcemia either from tumor such as myeloma and breast carcinoma (*3,4*), or from metabolic diseases such as renal insufficiency and milk-alkali syndrome (*5,6*). In both malignant and nonmalignant conditions, impaired renal function with consequent decreased phosphate excretion is a prerequisite for this phenomenon (*7*). Gastric uptake of [^{99m}Tc]MDP has been reported only once in a patient with vitamin D intoxication who had both lung and stomach accumulation (*7*). One other patient with vitamin D intoxication and elevated lung uptake has also been reported (*8*). No histologic proof of metastatic calcification was reported in these cases. Recently, we observed a massive concentration of [^{99m}Tc]MDP in the stomach of a patient due to vitamin D_3 abuse.

Vitamin D is easily obtainable and often used in large quantities. Bone scanning is not uncommonly used in the evaluation of hypercalcemia, therefore it is worthwhile to examine the observations noted in this patient.

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For reprints contact: Frans Corstens, MD, Dept. of Nuclear Medicine, St. Radboud University Hospital, Box 9101, 6500 HB Nijmegen, The Netherlands.

CASE REPORT

A 45-yr-old white woman had a variety of complaints: nausea, abdominal pain, constipation, anorexia, polydipsia, polyuria, nocturia, dysuria, pain in the legs, decreased muscle strength, paresthesia, agitation, and depression. These symptoms had been present for 3 mo and had worsened gradually. On physical examination she was mentally confused but well oriented. There was redness of the conjunctiva; ophthalmologic examination showed small, glass-like, crystal-clear particles within the palpebral fissure area of the bulbar conjunctiva. The aspect and localization of the particles were typical for precipitation of calcium phosphate salts. Laboratory tests revealed hypercalcemia (3.42 mmol/l), hyperphosphatemia (1.95 mmol/l) in the presence of an elevated serum creatinine (384 μmol/l). Serum alkaline and acid phosphatase activities were normal. Urinalysis revealed mild proteinuria. On the seventh day after admission a [^{99m}Tc]MDP bone scan was performed. At that time serum-calcium had been lowered to 2.79 mmol/l, whereas serum creatinine had dropped to 166 μmol/l and phosphate had normalized to 0.98 mmol/l due to treatment with forced diuresis and furosemide. The level of parathormone was normal (53 ng/100 ml) while serum 25-OH vitamin D_3 was 739 nmol/l (normal range 31–129 nmol/l). The combination of impaired renal function with a relatively low parathormone level and an extremely elevated 25-OH vitamin D_3 concentration in serum unequivocally proved the diagnosis of vitamin D_3 intoxication. After further questioning, the patient revealed that she ingested 2,000 U vitamin D daily, that her local physician injected her once a year with 600,000 U of vitamin D_3 and that she consumed several liters of milk daily. The gamma camera images showed impressive uptake in the stomach (Fig. 1) with elevated uptake in most of the periarticular regions (Fig. 2). There was no

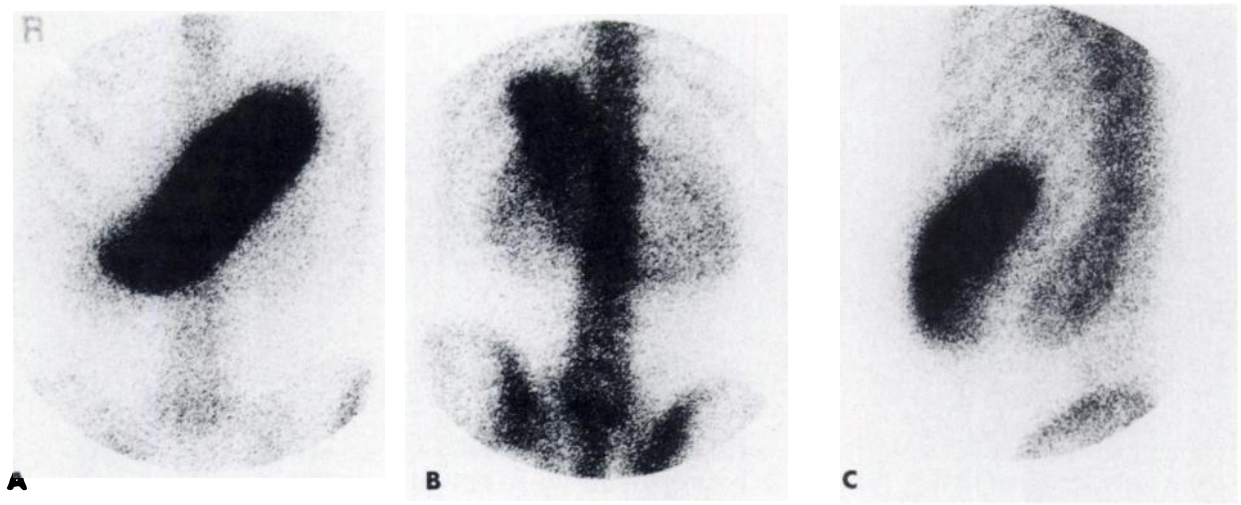

FIGURE 1
Initial bone scintigraphy: Accumulation of [^{99m}Tc]MDP in stomach visualized in anterior (A), posterior (B), and left lateral (C) position

elevated uptake in the lungs, and the thyroid was not visualized. Quality control of the radiopharmaceutical showed that the preparation was not contaminated with more than 0.5% of pertechnetate, as judged from ascending paper chromatography with 85% methanol on Whatman No. 1 paper. The labeled preparation was kept under nitrogen and was injected within 30 min after quality control. On gastroscopy, performed 2 days later, the mucosa of the stomach had a normal appearance. Histologic examination of biopsies, taken from the gastric body and pyloric antrum, showed well-developed mucosal glands, with—especially in the upper region of the acid-producing glands—multiple focal areas of fine granular and linear deposits along the basal cell borders and adjacent basement membranes. These deposits, hardly visible in the hematoxylin and eosin stain, were strongly positive in the Von Kossa and Dahl's Alizarin Red S stain. The positive results of both stains corresponded to calcium phosphate salts. The aspect of the deposits and the absence of any other histologic abnormality was typical for metastatic calcifications (Fig. 3).

A follow-up scan 18 days later, at which time the serum calcium and phosphate were normal and the creatinine had dropped to 90 μmol/l, showed no uptake in the stomach region.

DISCUSSION

Elevated stomach uptake of [^{99m}Tc]MDP can be due to free pertechnetate, to dystrophic, and to metastatic calcification. Localized uptake in the stomach region, which reportedly occurs in about 2% of consecutive bone scintigrams (*9*), is usually due to accumulation of free pertechnetate. It is unlikely that the gastric uptake in this patient resulted from secretion of free pertechnetate since the radiopharmaceutical was administered within 45 min after preparation, the quality control of the radiopharmaceutical was normal, and there was no thyroid or salivary uptake and no extra-osseous uptake found in other patients investigated on the same day using the same vial of labeled MDP. Elevated uptake of [^{99m}Tc]MDP in the stomach has also been reported in dialysis patients, possibly due to the formation of free pertechnetate in closed dialysis systems (*5*). Pathologic uptake of [^{99m}Tc]MDP in the stomach is usually secondary to dystrophic or metastatic calcification. Dystrophic calcifications occur in a variety of diseases, and are caused by deposition of calcium complexes in locally abnormal tissue. In our patient no structural abnormality was seen on histologic examination of the mucosa of the stomach.

Metastatic calcification occurs in the absence of underlying tissue abnormalities. In the last decade, several cases of metastatic gastric calcification detected by bone-scanning have been published. In a discussion of 16 cases with pulmonary metastatic calcifications positive on the bone scan, Rosenthal described eight patients with concomitant gastric uptake (*7*). One reportedly had vitamin D intoxication and localized Paget's disease.

Our patient had elevated uptake of [^{99m}Tc]MDP in the stomach, but no signs of elevated uptake in the lungs. Massive gastric uptake of [^{99m}Tc]MDP in the absence of elevated lung uptake has been reported only once previously; this was in a patient who had milk-alkali syndrome (*6*).

Elevated soft-tissue uptake of [^{99m}Tc]MDP caused by vitamin D intoxication has been reported twice (*7,8*). Histologic documentation of the metastatic calcification was not mentioned in these reports. The first patient described had elevated uptake in the lungs only, the second in both lungs and stomach. The latter patient reported (*7*), took, roughly estimated, 2,000 U/

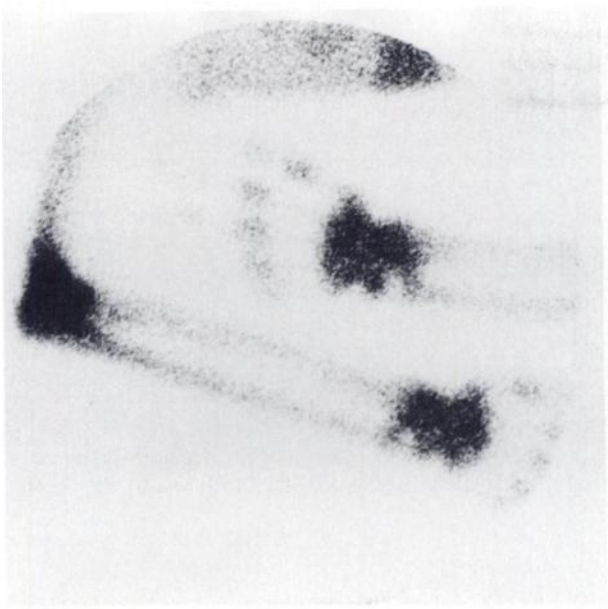

FIGURE 2
Initial bone scintigraphy: Accumulation of [^{99m}Tc]MDP in joints. Only scintigram of right arm and left hand are shown

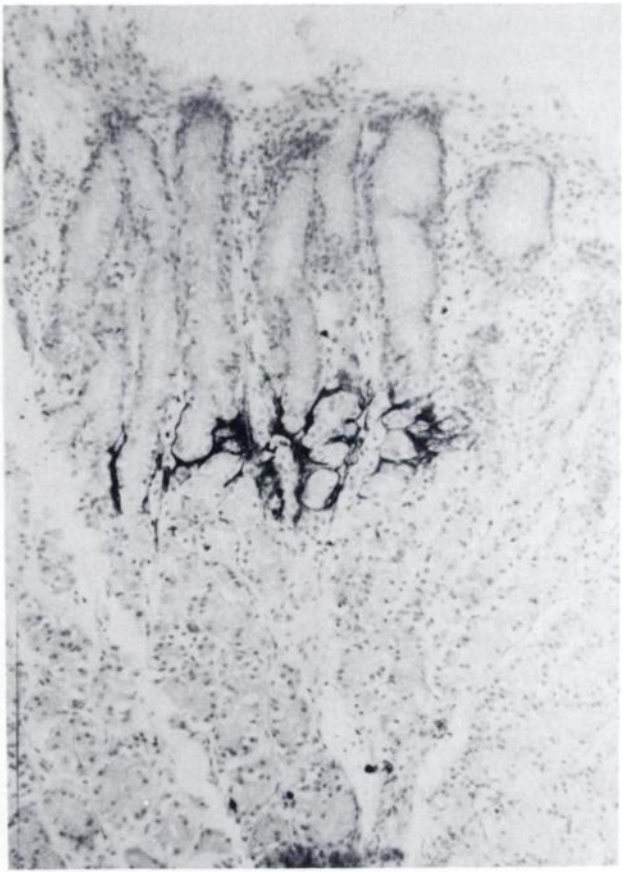

FIGURE 3
Von Kossa staining of gastric mucosal biopsy (160X), showing deposits around acid producing cells in tubular glands

day of vitamin D and 3 g/day of calcium. Our patient consumed 3–4 l of milk/day (~4 g calcium) in combination with ~2,000 U/day of vitamin D_3 orally, and 600,000 U/yr i.m. Though the intake of vitamin D was less than is usually considered to be toxic, it is likely that the addition of large amounts of calcium was sufficient to cause the combination of hypercalcemia and impaired renal function leading to metastatic calcification.

Calcium salts are more likely to precipitate in an alkaline environment. The secretion of acid leads to local alkalinity. The kidneys, the lungs, and the stomach are the three main organs in the body where acids are secreted. There is a local tissue alkalinity in the region of these acid producing cells, which has been suggested to predispose these tissues to metastatic calcification (*4*).

The exact mechanism of localization of the bone-seeking radiopharmaceuticals in metastatic calcifications is not understood. In hypercalcemia, visceral calcium deposits are initially amorphous calcium phosphate and are subsequently transformed into crystalline hydroxyapatite (*11,12*). Young amorphous calcium phosphate deposits have a larger adsorption surface, a higher hydration level and a greater rate of exchange than the relatively older crystalline apatite (*13*). These differences in physicochemical characteristics could explain the far higher [^{99m}Tc]MDP absorption capacity of newly formed amorphous calcium phosphate deposits as compared with metabolically less active apatite. In this patient, the second scan, after 3 wk of therapy, showed no extra-osseous uptake of [^{99m}Tc]MDP. Knowing the natural course of metastatic calcifications (e.g., in the eye) it is unlikely that the gastric calcifications shown on biopsy had disappeared in such a short time. With the normalization of both calcium and phosphate metabolism and improved kidney function, new formation of [^{99m}Tc]MDP avid amorphous calcium phosphate, had ceased.

This is the first reported observation, to our knowledge, of elevated [^{99m}Tc]MDP uptake solely in the stomach in a well-documented case of vitamin D intoxication, with resolution within 3 wk. In any case of elevated [^{99m}Tc]MDP uptake in the stomach and/or lungs, vitamin D intoxication should be considered. It is especially important to call attention to this observation, since a large number of "health food" tablets contain enough amounts of vitamin D and calcium to induce hypercalcemia and hyperphosphatemia with impaired renal function.

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