Parathyroid Carcinoma with Metastatic Calcification
Identified by Technetium-99m Methylene Diphosphonate Scintigraphy

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We describe herein a case of parathyroid carcinoma accompanied with metastatic calcification identified by technetium-99m methylene diphosphonate (Tc-99m MDP) scintigraphy in the lungs, kidneys and stomach. Parathyroid carcinoma remains a rare disorder despite the increased prevalence of primary hyperparathyroidism. Metastatic calcification is noted infrequently even in primary hyperparathyroidism and it may cause respiratory failure. Tc-99m MDP scintigraphy three months after surgery showed a complete disappearance of Tc-99m uptake in the stomach and an obvious reduction in the kidneys but no significant change in the lungs, indicating metastatic calcification can be reversibly reabsorbed. This case indicates that the adequate excision of parathyroid carcinoma as well as the early detection of metastatic calcification by Tc-99m MDP are obligatory.

(Key words: parathyroid, carcinoma, calcification, technetium-99m methylene diphosphonate (Tc-99m MDP)

Introduction

In spite of the increased prevalence of primary hyperparathyroidism with the advent of routine analysis of serum calcium and parathyroid hormone (PTH) assay, parathyroid carcinoma remains a rare disorder (1, 2). Metastatic calcification is known to be a long-term complication of renal failure accompanied with secondary hyperparathyroidism and to progress respiratory failure (3, 4). In primary hyperparathyroidism, however, metastatic calcification is noted infrequently (5).

We describe a rare case of parathyroid carcinoma accompanied with metastatic calcification identified by technetium-99m methylene diphosphonate (Tc-99m MDP) scintigraphy in the lungs, kidneys and stomach. Since metastatic calcification can be reversibly absorbed, not only the adequate excision of parathyroid carcinoma but also the early detection of metastatic calcification by Tc-99m MDP and the prevention of respiratory failure are obligatory and critical for the patient’s prognosis.

Case Report

A previously healthy 46-year-old woman presented with recent onset of profound hypercalcemia and somnolence. She had anorexia, nausea and vomiting in early January 1995. The persistence of these symptoms led her to consult a physician and she was admitted to another hospital on February 9, 1995, where the laboratory studies showed markedly elevated serum concentrations of calcium 4.9 mM, urea nitrogen (BUN) 19.6 mM and mildly elevated creatinine (Cr) 150.3 μM. She was referred to our hospital on March 4, 1995. The examination revealed a dehydrated woman in somnolence. There was a mass, 2 cm in diameter with elastic-firm consistency, at the left anterior neck which was not found in January. Laboratory data on admission to our hospital showed extreme hypercalcemia of 4.15 mM with remarkable hypercalciuria of 49.25 mmol/day and mild hyperphosphatemia, 1.55 mM, despite hyperphosphaturia of 47.13 mmol/day. Serum levels of BUN and Cr were mildly elevated to 10.7 mM and 106 μM, respectively. Creatinine clearance was markedly decreased to 28.6 ml/min. Other serum electrolytes such as sodium, potassium, chloride and magnesium were within the normal ranges (134, 3.4, 94 and 0.45 mM, respectively.)
respectively). The serum level of intact-PTH (i-PTH) was markedly elevated to 136.8 pM. Intact osteocalcin, a marker of osteoblastic activity, was elevated to 14.0 nM. The level of 1,25-(OH)2-vitamin D3 was 26.5 pM. The urinary levels of pyridinoline and deoxy-pyridinoline, markers of bone resorption, were markedly elevated to 339 and 82.5 pmol/μmol Cr, respectively. Nephrogenous cAMP was increased to 13.3 nmol/dl GFR and the renal tubular reabsorption of phosphate was decreased to 66%. The determination of arterial-blood gas disclosed partial pressure of oxygen 74.4 mmHg, partial pressure of carbon dioxide 39.6 mmHg, pH 7.41, and bicarbonate 24.3 mM. Ultrasonography and computed tomography of the neck demonstrated a mass consistent with the left lower parathyroid gland. Radiothallium-technetium subtractive scintigraphy showed an uptake at the left lower parathyroid gland. The roentgenograms of the chest, hands and feet were normal. Computed tomography of the lung showed questionable ground-glass opacities in both lower lobes. Tc-99m MDP scintigraphy demonstrated a markedly increased uptake of the radionuclide in the lungs, kidneys and stomach (Fig. 1). The removal of the left lower parathyroid gland and left lobectomy of the thyroid gland were performed on March 9, 1995. Microscopical examination of the removed parathyroid gland showed carcinoma of the parathyroid gland characterized by atypical chief cells with large nuclei and abundant mitoses as shown in Fig. 2; it was also characterized by perivascular palisading and invasion into the capsule and the vasculature of the adjacent areas. Furthermore, the presence of local invasion spreading to the thyroid gland and regional lymph nodes was noticed. On the first postoperative day, the i-PTH fell to 1.8 pM and serum calcium concentration decreased to 2.5 mM by the third postoperative day. The second Tc-99m MDP scintigraphy (Fig. 3), performed three months after surgery, demonstrated the complete disappearance of Tc-99m uptake in the stomach and a marked reduction of uptake in the kidneys. In contrast, no significant change in Tc-99m uptake in the lungs was noticed. Pulmonary function tests performed one month after surgery showed a vital capacity of 1.42 l, 55.25% of the predicted value and the forced expiratory volume in one-second was 1.16 l, 84.67% of the predicted value. The carbon monoxide diffusing capacity could not be measured as the vital capacity was too small.

Discussion

The prevalence of primary hyperparathyroidism appears to have increased with the advent of more widespread recognition of the disorder and with routine analysis of serum calcium; it is estimated to occur in approximately 0.1% of general population (1, 2). On the other hand, parathyroid carcinoma remains rare and has accounted for only 3 to 4% of the cases of hyperparathyroidism in most series (6). However, since the incidence of parathyroid carcinoma has not increased appreciably during a time when benign parathyroid disease has increased dramatically, parathyroid carcinoma might be an even more unusual cause of PTH-dependent hypercalcemia than it used to be.

Figure 1. Preoperative Tc-99m MDP scintigraphy. The preoperative Tc-99m MDP scintigraphy demonstrated remarkable Tc-99m MDP uptake in the lungs, kidneys and stomach. The anterior view is shown on the left and the posterior view on the right.

Figure 2. Light microscopy of the parathyroid gland. Light microscopy of the parathyroid gland showed atypical chief cells with large nuclei and abundant mitoses (HE stain, ×400).
Shane and Bilezikian suggested that the incidence of parathyroid carcinoma of 0.1% to 1% of primary hyperparathyroidism seems to be a more accurate estimation (1). The case presented here showed extremely high serum levels of calcium and i-PTH and a palpable mass in the neck, being compatible with the characteristics of parathyroid carcinoma reported previously. Although parathyroid carcinoma tends to be slow-growing (1, 2, 7), the mass of parathyroid carcinoma in this case grew very rapidly in a month and symptoms progressed abruptly, reflecting the deviant nature of malignancy shown by abundant mitoses and local invasion.

Noteworthy in this case is that metastatic calcification was identified in the lungs, kidneys and stomach by Tc-99m MDP scintigraphy. Metastatic calcification is known to be a long-term complication that occurs in patients with chronic renal failure accompanied with secondary hyperparathyroidism (3, 4). It has been noted, however, that primary hyperparathyroidism produces metastatic calcification infrequently, the figures of its incidence being not compiled. As far as we are aware, metastatic calcification in parathyroid carcinoma identified by Tc-99m MDP was reported in only one case (8). Metastatic calcification tends to occur when the solubility product for calcium and phosphate exceeds 60 (both in mg/dl) (3, 4). In this situation, the Tc-99m MDP concentration in tissues is proportional to their calcium content and MDP acts as a ligand adsorbing onto the surface of the hydroxyapatite crystal of the tissue, localizing the Tc-99m in the mineral phase with no significant organic substrate interaction (9). Furthermore, it has been known that alkaline milieu enhances calcium-phosphate deposition in metastatic calcification. The relative alkalinity of alveolar walls, renal tubules and gastric mucosa leads to the greater frequency of Tc-99m MDP and calcium salt localization in the lungs, kidneys and stomach (10). On the basis of this, Tc-99m MDP has been used extensively to image metastatic calcification since metastatic calcification is hardly detected by conventional radiography (11).

Serum phosphate level in primary hyperparathyroidism is relatively low due to the phosphaturic effect of circulating PTH, so that the product of calcium and phosphate is generally less than 60, as a consequence metastatic calcification is rarely seen, and the same is also true of parathyroid carcinoma accompanied with high serum levels of calcium and PTH. The possible reasons for metastatic calcification in the present case would be the extremely high serum calcium level and mildly elevated serum phosphate level, which resulted in a very large value of product of calcium and phosphate (79.6, calculated in mg/dl). The mild elevation of the serum phosphate level was induced probably not only by the large load of phosphate from the increased bone resorption by the action of remarkably elevated circulating i-PTH but also by phosphate retention which resulted from dehydration and prerenal failure indicated by the decreased glomerular filtration rate and high BUN to Cr ratio, overcoming the lowered tubular reabsorption of phosphate.

Parathyroid carcinoma usually spreads locally to contiguous structures as in the present case, followed later by distant metastases such as the lung and liver (1, 2), which can be detected by conventional radiography and/or CT scan. It is unlikely in this case, however, that parathyroid carcinoma metastasized to both lungs, resulting in marked Tc-99m MDP uptake, since Tc-99m MDP scintigraphy showed strikingly uniform, symmetrical and intense radioactivity in both lungs, conventional radiography and CT scan could not detect metastatic calcification or any abnormal solid masses, and parathyroid carcinoma of the neck itself did not show any Tc-99m MDP uptake. Pulmonary metastatic calcification always begins in the basement membranes of the epithelium and endothelium of alveoli, spreading to involve surrounding alveolar connective tissues and then blood vessels as it becomes more severe (5), although the histologic confirmation of metastatic calcification using the transbronchial lung biopsy could not be performed in this case due to the patient’s refusal. In accord with a previous report (4), the pulmonary function study showed a decrease in the vital capacity, the carbon monoxide diffusion capacity and the blood oxygen level.

Tc-99m MDP uptake was also remarkable in the stomach.
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and kidneys. It is unlikely, however, that free pertechnetate secreted from the stomach and kidneys was visualized, since the lack of Tc-99m uptake in the thyroid, salivary glands and urinary bladder excluded the in vivo free pertechnetate. Tc-99m MDP scintigraphy three months after surgery showed the complete disappearance of Tc-99m MDP uptake in the stomach and an obvious reduction in the kidneys but there was no significant change in the lungs. Metastatic calcification has been seen within the lamina propria of the stomach, in tubules and interstitium of the kidneys, and in basement membranes of the epithelium and endothelium of alveoli in the lungs (12). The turnover rate of cells of calcium-phosphate deposited sites is fastest in cells of the gastric wall, intermediate in those of renal tubules and slowest in those of basement membranes of alveoli. This is the possible reason that Tc-99m MDP uptake disappeared first in the stomach, was reduced in the kidneys and remained unchanged in the lungs. Although most patients with metastatic pulmonary calcification are typically asymptomatic, respiratory failure may develop and cause death in the far advanced stage (13, 14). Since metastatic calcification can be reversibly absorbed by appropriate therapy (15) as shown by postoperative Tc-99m MDP scintigraphy, the detection and prevention of this complication are very critical for the prognosis of such patients.

The present case indicates that adequate excision of parathyroid carcinoma as well as early detection of metastatic calcification by Tc-99m MDP are obligatory for preventing the recurrence of parathyroid carcinoma and the development of respiratory failure.

References