Successful Treatment by Surgical Removal of Bone Metastasis Producing PTH: New Approach to the Management of Metastatic Parathyroid Carcinoma

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A 62-year-old woman had primary hyperparathyroidism due to parathyroid carcinoma. In spite of surgical removal of the enlarged parathyroid gland, intractable hypercalcemia persisted. 99mTc-methoxyisobutylisonitrile scanning revealed bone metastatic lesions, although conventional 201Tl-chloride scanning failed to demonstrate those lesions. Octreotide inhibited parathyroid hormone (PTH) secretion, although various means such as bisphosphonates, calcitonin and hydration were effective to reduce serum calcium level to some extent but failed to reduce PTH secretion at all. The CT-guided transcutaneous tumor marking facilitated the subsequent orthopedic surgery for successful removal of the metastatic focus of PTH secretion from the iliac bone. (Internal Medicine 33: 697-702, 1994)

Key words: Tc-methoxyisobutylisonitrile (99mTc-MIBI), octreotide, CT-guided tumor marking

Introduction

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism; it’s reported incidence ranges between less than 0.1% and 5% (1-4). Morbidity of the disease results from the effects of unremitting hypercalcemia caused by the production of parathyroid hormone (PTH) by the tumor rather than by infiltration of carcinoma into vital organs. Although the most effective treatment of parathyroid carcinoma remains to be a surgical approach (1, 3-5), surgery is not always possible or successful, especially if the carcinoma has multiple metastases. The most effective way for management of metastatic parathyroid carcinoma remains to be determined (6). We approached the issue with novel techniques, which include 99mTc-methoxyisobutylisonitrile (MIBI) imaging, therapy with the long-acting somatostatin analogue, octreotide, and computed tomography (CT) scan-guided transcutaneous marking and subsequent surgical resection.

Case Report

A 58-year-old Indonesian woman with Chinese extraction was admitted to Mount Elizabeth Medical Center, Singapore, in October 1990, because of hypercalcemia (12.9 mg/dl), constipation and loss of appetite. The serum parathyroid hormone (PTH) concentration was 91.1 ng/dl (normal up to 27 ng/dl, mid-region assay). The ultrasonography and magnetic resonance imaging of the neck with special reference to the thyroid gland and bilateral superior and inferior thyroid arteriography were carried out. These examinations suggested that the patient suffered from primary hyperparathyroidism due to enlarged right upper parathyroid gland. On November 23, 1990, the patient underwent an exploration surgery at Mount Elizabeth Medical Center. Tibbin’s right unilateral parathyroidectomy was carried out. There was a firm lesion, 1.5x1.2x1.0 cm of the superior parathyroid gland. The lesion was adherent to the back of the upper pole of the thyroid with a large amount of fibrous tissue. The inferior parathyroid gland was normally situated at the classical position. Clinically, parathyroid carcinoma was suspected. Finally, histological examination including overseas consultation confirmed a parathyroid carcinoma of the superior and normal parathyroid tissue of the inferior gland. Immediately following the operation, the serum calcium level fell and she required calcium supplements. PTH levels also returned to normal.

The serum calcium and the PTH levels remained normal...
until May 1993, when the levels of calcium and intact PTH were 13.2 mg/dl and 136.0 pg/ml (normal range 10 pg/ml–65 pg/ml), respectively. The patient complained of fatigue, lassitude and loss of appetite and was referred to us at Toranomon Hospital, Tokyo in July 1993. She was treated with saline infusion and administration of bisphosphonates and calcitonin, because serum calcium levels were seriously high (ranging from 14 mg/dl to 17 mg/dl). Ultrasonography, CT scan, Thallium(Tl)-201/Technetium (Tc)-99m pertechnetate subtraction imaging and 201Tl-chloride scanning with single photon emission computed tomography (SPECT) imaging showed questionable foci in right cervical region and center of upper mediastinum. Venous sampling showed an elevation of intact PTH from inferior thyroid vein as high as 700 pg/ml (and that from vena cava was 624 pg/ml). Lungs were free from pathology either on X-ray and CT scan. On August 11, 1993 a total thyroidectomy and a thorough dissection of the tracheal and esophageal region and a mediastinal exploration were performed, but no residual tumor was detected. There was no carcinoma in the resected specimens. Intact PTH levels remained elevated after surgery (Fig. 1).

Then, a series of localization studies was performed again.

Although 201Tl-chloride scintiscanning with planar imaging showed no abnormal deposits, 99mTc-MIBI scanning with planar and SPECT imaging revealed abnormal accumulation at the third lumbar vertebra and the right iliac bone (Fig. 2A). CT scan revealed mass lesions (Fig. 2B) and digital subtraction aortography demonstrated tumor stains corresponding to 99mTc-MIBI accumulation. Bone scintigraphy (99mTc-hydroxymethylene diphosphate) failed to show lesions. A selective

Fig. 2. A) 99mTc-MIBI scanning demonstrates abnormal accumulation in the third lumbar vertebra and iliac bone (arrows). B) Computed tomography shows metastatic parathyroid carcinoma in the third lumbar vertebra and iliac bone (arrows).
venous sampling for intact PTH revealed high PTH levels in the left iliac vein and the lower inferior vena cava (Fig. 3). Bisphosphonates were very effective in controlling hypercalcemia without side effects, but their effects were quickly counteracted by the gross increase in intact PTH level. Next we examined the effect of octreotide on PTH production of parathyroid carcinoma. Octreotide was administered as a subcutaneous dose of 200 μg at 9.00 h. At the beginning of treatment, intact PTH level was 919 pg/ml. After subcutaneous injection of octreotide, there was a decrease in PTH to 812 pg/ml at 2 hours. By 5 hours after injection, the PTH level began to rise and by 6 hours, values had returned to near pretreatment level. It is suggested that the duration of suppressive action was approximately 5 hours. At the same time there was a decrease in growth hormone during 4 hours (Fig. 4), demonstrating the suppressive effect of octreotide. Then, we used octreotide to suppress PTH levels before a second operation. The subcutaneous administration of octreotide, 100 μg every 8 hours for 7 days, suppressed PTH levels, which fell from a pretreatment level of 1,447 pg/ml to 1,164 pg/ml, without side effects (Fig. 1). However, we could not evaluate the effect of treatment on the serum calcium level, because at the same time, a bisphosphonate, alendronate, or calcitonin, it was essential to avoid a hypercalcemia crisis, thus was administrated separately or combination. Octreotide treatment was discontinued after 7 days. PTH rose to 1,733 pg/ml within 5 days after interruption of the treatment.

On September 29, 1993, orthopedic surgery was successfully carried out on the third lumbar vertebra. At operation, a 2 cm tumor was found on the third vertebral body. The tumor was soft and dark gray and had a thin capsule. The patient had undergone en bloc resection of the tumor. Histopathologic examination confirmed the diagnosis of metastatic parathyroid carcinoma (Fig. 5). Microscopically the tumor was composed of small cells with uniform nuclei, occasional tubular structures and mitosis. Rapid intact PTH measurement carried out on site during surgery demonstrated an abrupt decrease in the PTH level (from 1,476 pg/ml to 463 pg/ml, normal ranging from 20 pg/ml to 53 pg/ml). Then, a right ilium exploration was performed. The right posterior iliac wing was apparently normal on inspection. The portion which seemed to coincide with the 99mTc-MIBI spot was blindly resected, but no pathologic lesions were histologically detected. There was no carcinoma in the bone specimens and the intact PTH level was not changed (from 463.0 pg/ml to 462.7 pg/ml) with rapid on site assay.

**Fig. 3.** Intact parathyroid hormone value (pg/ml) obtained from blood samples drawn during the selective venous catheterization. High hormone levels in the left iliac vein and the lower inferior vena cava were found on two occasions (underlined). Normal range is 20 pg/ml to 53 pg/ml.

**Fig. 4.** Intact parathyroid hormone (○), growth hormone (■) and thyrotropin (■) after subcutaneous injection of 200 μg of octreotide. For the convenience of comparison, basal value is taken as 100% for growth hormone and thyrotropin.
After the operation, the PTH level decreased to 318 pg/ml on the third postsurgical day. Since then, her serum calcium and intact PTH became elevated (Fig. 1). $^{99m}$Tc-MIBI scanning with SPECT imaging revealed an abnormal accumulation at the previously revealed site in the right iliac bone, which was larger in size.

It is difficult to find the iliac bone lesion during surgery without a marking method unless the compact bone of the surface is invaded. Thus, preoperative CT-guided tumor marking was performed (Fig. 6). A similar technique for bone biopsies has been reported earlier (7, 8). Initially, a sterile radiopaque grid was placed over the puncture area and a CT scan was obtained to select the optimum puncture site, puncture angle and distance. The puncture site was indicated on the skin and local anesthesia was performed. A 21-gauge needle was introduced through the skin and into the tumor. Another CT scan was obtained to localize the tip of the needle. When the needle was positioned correctly in the tumor, 0.5 ml of a mixture of iopamidol and methylrosaniline chloride was injected into the tumor. The intact PTH level fell significantly from 1,010 pg/ml to 189 pg/ml probably due to the toxic effect of the contrast medium and marking dye. The marking showed an ablation effect, unexpectedly.

A third operation was undertaken at which time the right posterior superior iliac spine which was stained with methylrosaniline chloride was partially resected. On histological examination, carcinoma was found in the excised bone specimens. The intact PTH levels decreased to the undetectable range (Fig. 1). An abnormal accumulation in the right iliac bone disappeared with $^{99m}$Tc-MIBI scanning carried out after surgery. Initially the patient required vitamin D derivatives and oral calcium to maintain normal serum calcium levels. She is currently well without any evidence of further recurrence.

Fig. 5. Microphotograph shows a lumbar spine metastasis of parathyroid carcinoma and surrounding bone tissues (HE stain, ×50).

Fig. 6. The CT scan reveals a tumor 1 cm in diameter in the iliac bone, which was penetrated with 21-gauge needle (black arrow). Through the needle, a mixture of iopamidol and methylrosaniline chloride was injected. The white arrow indicates to the bone defect for a second operation.
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Discussion

The best way of management of metastatic parathyroid carcinoma remains to be determined (6). Before any surgical resection is attempted, localization of the lesion is essential. However, vigorous attempts often fail to localize lesions. Innovation in this aspect is currently available, namely, imaging of metastatic parathyroid carcinoma by means of $^{99m}$Tc-MIBI scanning and CT-guided marking.

Although $^{201}$Tl-chloride scintiscanning has been the standard nuclear medicine study for locating metastasis (1, 6), we had no information concerning special localization by $^{201}$Tl-chloride scanning with planar imaging before the second operation. $^{99m}$Tc-MIBI has recently been introduced for myocardial perfusion imaging as an alternative to $^{201}$Tl-chloride. The 140 KeV photon energy of $^{99m}$Tc-MIBI is optimal for gamma camera imaging and is more likely to produce high quality images. The half-life of $^{99m}$Tc and dosimetry of $^{99m}$Tc-MIBI make it possible to administer a dose of radiopharmaceutical 10–15 times higher than that of $^{201}$Tl. This results in better images within shorter time and is ideally suited for SPECT (9). $^{99m}$Tc-MIBI shows great promise in the purpose of location of sites of parathyroid tissue (10–12). In the case of $^{201}$Tl, its low energy emission would preclude scanning deep sources, such as substernal and distant metastasis. In the present case, $^{99m}$Tc-MIBI scanning revealed bone metastatic lesions, although $^{201}$Tl-chloride scanning failed to demonstrate the lesions. Based on the physical and biological properties, $^{99m}$Tc-MIBI may replace $^{201}$Tl-chloride for localization of metastatic parathyroid carcinoma.

We used the CT-guided technique for marking the tumor position before a third operation (Fig. 6). After marking the lesion, the tumor was stained and orthopedic surgery to remove the metastasis was successfully carried out. If surgically accessible, CT-guided marking and surgical resection may be an effective therapy for the bone metastases of parathyroid carcinoma as typically demonstrated in the present case.

The most effective treatment for parathyroid carcinoma is complete surgical excision. Unfortunately, surgery is not always possible or successful, especially when the carcinoma has metastasized. In this instance, another approach to control tumor growth or inhibit PTH secretion must be considered. However, irradiation therapy is usually ineffective (3, 13), and chemotherapy has not benefitted most patients with parathyroid carcinoma (1, 5, 14).

The long-acting somatostatin analogue octreotide is characterized as a regulatory-inhibitory peptide with endocrine activity. The general inhibitory function of octreotide is wide ranging and affects a number of organ systems (15). A recent report documented octreotide treatment for hypercalcemia associated with a parathyroid adenoma (16), a pancreatic islet cell tumor (17) and a pheochromocytoma (18). A dose of octreotide of between 50 μg and 250 μg twice a day was successful in decreasing the serum calcium and PTH or parathyroid hormone-related peptide. Unlike some of the other drugs used to lower serum calcium levels, octreotide is readily available to administer and relatively free of side effects. As shown in the results, we have demonstrated the beneficial effects of octreotide on PTH secretion from a parathyroid carcinoma which has not been reported previously. Bisphosphonates have been very effective in controlling hypercalcemia associated with malignancy, including parathyroid carcinoma (1, 5) and primary hyperparathyroidism (19), almost without side effects and they have prolonged effectiveness by inhibiting bone resorption. But bisphosphonates are ineffective in reducing PTH production. Other means such as rehydration, calcitonin, plicamycin or gallium nitrate are also ineffective in this regard. Only octreotide is effective in controlling PTH production. In the present case, we observed a fall in PTH level during short duration of treatment with octreotide. Fortunately, we needed not use further octreotide treatment because of successful surgery. However, long duration therapy of octreotide may be worthwhile in cases when surgical removal is not successful.

After preoperative CT-guided tumor marking was performed, the intact PTH level significantly fell. For parathyroid adenoma, fine needle percutaneous tumor impalement and intratumoral injection of ethanol guided by ultrasonography or CT have been published (20, 21). Percutaneous CT-guided ablation technique is likely also useful for inoperative metastatic parathyroid carcinoma.

$^{99m}$Tc-MIBI scanning, CT-guided marking and octreotide may be effective in the management of metastatic parathyroid carcinoma, and they are worthy of attempt for this disease.

Acknowledgements: We thank Dr. Daishu Miura and Dr. Mika Kawai for their assistance with the surgery. We are indebted to Dr. Yutaka Ozaki, Dr. Noboru Shindou and Dr. Atsuko Kurowski who performed CT scan and angiography, and to Dr. Hirota Maruno who performed scintigraphy.

References


