A Patient with Classic Severe Primary Hyperparathyroidism in Whom both Tc-99m MIBI Scintigraphy and FDG-PET Failed to Detect the Parathyroid Tumor

Kaori SEKI, Koshi HASHIMOTO, Takeshi HISA, Masaki MAEDA, Tetru SATOH, Yutaka UEHARA, Hiroshi MATSUMOTO*, Tetsunari OYAMA**, Masanobu YAMADA and Masatomo MORI

Abstract

A 24-year-old woman was admitted to our department for further examination of hypercalcemia, a high level of intact parathyroid hormone (PTH) and a right parathyroid tumor. She complained of bone pain throughout her body and was unable to walk due to systemic cystic osteofibrosis, including a brown tumor of the left lower extremities. Neck ultrasonography (US) and magnetic resonance imaging (MRI) revealed a tumor 2 cm in diameter in the upper side of the right thyroid lobe. $^{99m}$Tc sestamibi ($^{99m}$Tc-MIBI) imaging and F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) were performed to diagnose primary hyperparathyroidism and examination of other parathyroid glands. However, neither imaging modality detected the parathyroid tumor. To confirm the diagnosis, we performed selective venous sampling around the parathyroid and the patient was diagnosed with primary hyperparathyroidism due to a right parathyroid tumor. Resection of the right parathyroid tumor was performed and the pathological diagnosis was parathyroid adenoma. To date, both $^{99m}$Tc-MIBI and FDG-PET are useful to localize parathyroid tumors. In this case, however, neither modality detected the tumor. Although recent studies state that expression of P-glycoprotein (P-gp) in parathyroid tumors plays an important role in the false-negative results of both $^{99m}$Tc-MIBI and FDG-PET, immunohistological study detected no P-gp expression in the parathyroid tumor in the current case.

(Key words: primary hyperparathyroidism (PHPT), $^{99m}$Tc-MIBI, FDG-PET, P-glycoprotein (P-gp))

Introduction

Primary hyperparathyroidism (PHPT) is a condition characterized by an excess secretion of parathyroid hormone by adenomatous or hyperplastic glands, and between 80% and 95% of patients with hyperparathyroidism have a solitary adenoma of the parathyroid glands (1). PHPT is a relatively common disorder, especially among the elderly. Epidemiological studies traditionally have found incidence rates in the range of 25–28 cases/100,000 population annually (1–4). Operative removal of hyperfunctioning parathyroid tissue by an experienced endocrine surgeon achieves permanent relief in 85% to 90% of initial neck explorations (5, 6). Thus, accurate preoperative localization of parathyroid adenoma is important to reduce the operative failure rate (7). Techniques including high-resolution ultrasonic (US) study, computerized tomography (CT), and magnetic resonance imaging (MRI) are commonly used for this purpose, although all three modalities have some limitations (8, 9). A major advance was a nuclear medicine technique with TI-201/[Tc-99m]-pertechnetate subtraction scanning, which was introduced for parathyroid localization (10). However, there has been no consensus on the sensitivity and specificity of the scan (11, 12). Recently, the $^{99m}$Tc sestamibi (Tc-99m MIBI) parathyroid scan was described as an alternative to TI-201/[Tc-99m]-pertechnetate subtraction scanning, which was introduced for parathyroid localization (10). However, there has been no consensus on the sensitivity and specificity of the scan (11, 12). Recently, the $^{99m}$Tc sestamibi (Tc-99m MIBI) parathyroid scan was described as an alternative to TI-201/[Tc-99m]-pertechnetate subtraction scanning for parathyroid localization (13–17). Tc-99m MIBI is a lipophilic cationic complex, which was originally introduced for myocardial perfusion scintigraphy (18). Tc-99m MIBI has biological properties similar to TI-201 for evaluation of viability of cells and lesions. However, it has advantages of superior physical properties of Tc-99m and a higher target-to-background ratio than TI-201 (19). Tc-99m MIBI is localized in the thyroid and parathyroid glands, but it washes out of...
the thyroid faster than the parathyroid, thus providing a greater parathyroid-to-thyroid uptake ratio with time. Therefore, Tc-99m MIBI appears useful for localization of the parathyroid with either a subtraction procedure or indeed as a sole agent (15, 20). However, the exact mechanisms of visualization of abnormal and hyperfunctioning parathyroid tissue are not clear. On the other hand, F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) was recently introduced as a powerful tool to detect tumors, especially malignant tumors, because most tumoral cells demonstrate increased glucose metabolism which is due, in part, to an increased number of glucose transporter proteins (21). We can also evaluate the malignancy of the tumors with standard uptake value (SUV) levels. There are some reports that demonstrate the usefulness of FDG-PET to detect parathyroid tumors (21–25). In this report, we present a rare case of classical severe PHPT, in which neither Tc-99m MIBI nor FDG-PET detected the parathyroid tumor, even though physical examination, ultrasonography and MR imaging clearly showed the tumor. We also examine the expression of P-glycoprotein (P-gp) of the parathyroid adenoma and discuss the correlation between P-gp expression and Tc-99m MIBI imaging.

Materials and Methods

Immunohistochemical study

Paraffin sections of 4 μm-thickness were cut from archival paraffin blocks containing a representative histology of the lesion. An immunohistochemical study was performed on the sections using the avidin-biotinylated peroxidase complex (ABC) method with the anti-MDR (P-glycoprotein) monoclonal antibody (SC-13131, Santa Cruz, CA, USA) at 1:50 dilution magnification. Briefly, paraffin sections were dewaxed with xylene and incubated with 0.3% hydrogen peroxide in absolute methanol to block endogenous peroxidase activity. To avoid non-specific staining, the sections were incubated with 10% normal horse serum for 30 minutes at room temperature and treated with the primary antibody at 4 °C overnight. After intensive washing, the sections were incubated with the secondary biotinylated anti-mouse or rabbit IgG (Vector Laboratories, Burlingame, CA, USA) for 30 minutes at room temperature, followed by incubation with the ABC complex (Dako Cytomation Co., Ltd., Glostrup, Denmark) for 30 minutes at room temperature. Finally, the slides were visualized with a solution containing 0.02% 3,3’-diaminobenzidine tetrahydrochloride and 0.005% H2O2, followed by light counterstaining with hematoxylin. As a positive control, adrenal cortical adenoma sections were employed.

Case Report

A 24-year-old woman was referred and admitted to our department for further examination of hypercalcemia, an extremely high level of intact parathyroid hormone (PTH) and a right parathyroid tumor. She complained of lumbago during pregnancy one year before admission and visited another hospital. Although her serum alkaline phosphatase (ALP) level was elevated at the time of the visit, she was told that it was due to pregnancy and was diagnosed with bilateral renal stones. After delivery of her first child three months before admission, she was not able to walk or even to stand up because of bone pain in the left lower extremities. She was referred to Maebashi Kyoritsu Hospital for further examination and hypercalcemia with a high level of serum intact PTH and right neck mass were detected. On admission, the patient’s serum calcium and intact PTH level were 12.7 mg/dl and more than 1,000 pg/ml, respectively (Table 1). A solid mass was palpable at the right side of the neck. She complained of bone pain throughout her whole body and was unable to walk. The X-ray study demonstrated a ‘salt and pepper’ appearance in the cranium and generalized demineralization of bone, including ‘brown tumors’ in the left lower extremities. Nephrocalcinosis was found in the bilateral kidney on plain abdominal radiographs (Fig. 1). These findings led us to diagnose the patient with classical severe primary hyperparathyroidism. Neck ultrasonography (US) revealed a tumor 2 cm in diameter in the upper side of right thyroid lobe. The tumor was iso-echoic and almost homogeneous inside. Color Doppler US demonstrated plentiful pulsating blood flow (Fig. 2). MRI allowed identification of a parathyroid tumor which showed a low to intermediate signal intensity on T1-weighted images and a high signal intensity on T2 images compared with the surrounding tissues (Fig. 2). Tc-MIBI scintigraphy and FDG-PET were performed to diagnose primary hyperparathyroidism and examination of other parathyroid glands. However, unexpectedly, both imaging modalities failed to detect the parathyroid tumor (Fig. 3). Although it appeared that the tumor in the upper side of right thyroid lobe was the origin of this disorder, we performed selective venous sampling for intact PTH measurement around the parathyroid to rule out an ectopic PTH producing tumor and to ensure the efficacy of surgical resection of the tumor. As shown in Fig. 4, there was no significant difference between the right and left sides of the jugular vein, however, the maximum point of intact PTH was the right superior thyroid vein (Fig. 4). Thus, according to the results of the venous sampling, the preoperative localization of the parathyroid tumor was in the upper right side of the neck as US and MRI imaging indicated. Resection of the right parathyroid tumor was performed and the pathological diagnosis was parathyroid adenoma (Fig. 5A, B). Immunohistological study revealed that the parathyroid adenoma did not express P-glycoprotein (P-gp) (Fig. 5C). Soon after the operation, her serum calcium levels were restored to the normal range. After that, because of ‘hungry bone’ syndrome, her serum calcium levels decreased to 6.4 mg/dl and her intact PTH levels increased to 197 pg/ml (Fig. 6). Four microgram of alfalcacidol and 2.4 g of calcium L-aspartate were administered to her to maintain her serum calcium levels. Two months after the operation, the patient’s bone pain complete-
Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Blood chemistry</th>
<th>Tumor marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct 33.4%</td>
<td>TP 7.8 g/dl</td>
<td>CEA &lt;0.1 ng/ml</td>
</tr>
<tr>
<td>Hb 10.6 g/dl</td>
<td>Alb 4.2 g/dl</td>
<td>SCC 1.1 ng/ml</td>
</tr>
<tr>
<td>RBC 369×10^4/µl</td>
<td>T-bil 0.5 mg/dl</td>
<td>NSE 6.7 ng/ml</td>
</tr>
<tr>
<td>WBC 14,500/µl</td>
<td>AST 25 IU/l</td>
<td>CA 19-9 26 U/ml</td>
</tr>
<tr>
<td>Neu. 9,210/µl</td>
<td>ALT 14 IU/l</td>
<td>CA 125 &lt;6 U/ml</td>
</tr>
<tr>
<td>Lym. 2,480/µl</td>
<td>LDH 127 IU/l</td>
<td></td>
</tr>
<tr>
<td>Eos. 1,800/µl</td>
<td>ALP 6,955 IU/l</td>
<td>osteocarcin 215 ng/ml</td>
</tr>
<tr>
<td>Bas. 50/µl</td>
<td>ALP2 223.3%</td>
<td>Intact-PTH &gt;1,000 pg/ml</td>
</tr>
<tr>
<td>Mon. 780/µl</td>
<td>ALP3 376.7%</td>
<td>calcitonin 13 pg/ml</td>
</tr>
<tr>
<td>PLT 45.3×10^4/µl</td>
<td>LAP 831 IU/l</td>
<td>1,25 (OH)D 81.2 pg/ml</td>
</tr>
<tr>
<td></td>
<td>CPK 321 IU/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AMY 428 IU/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BUN 17 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cr 0.6 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Na 137 mEq/l</td>
<td>u-Ca 259.2 mg/day</td>
</tr>
<tr>
<td></td>
<td>K 4.7 mEq/l</td>
<td>CCr 48.1 ml/min</td>
</tr>
<tr>
<td></td>
<td>Cl 106 mEq/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P 1.6 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ca 12.7 mg/dl</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. X-ray studies of the whole body. A) Skull X-ray showing ‘salt and pepper’ appearance (arrowhead) and osteolysis (arrows). B) Left lower extremities showed a ‘brown tumor’ (arrowheads). C) Nephrocalcinosis was found in the bilateral kidney on plain abdominal radiographs (arrowheads). D) Osteolysis was found in the right fourth finger (arrow).
ly disappeared and she became able to walk.

**Discussion**

We encountered a case of classical severe PHPT. The patient had complained of lumbago and a blood test demonstrated high levels of serum alkaline phosphatase during her first pregnancy about one year before admission. However, in another hospital, she was told that it was due to pregnancy. We speculate that her serum calcium levels were already high at that time and this misdiagnosis led her to develop classical severe PHPT. We should consider PHPT as a differential diagnosis and measure serum calcium levels when we encounter similar patients. To date, both \(^{99m}\)Tc-MIBI and FDG-PET have been useful to localize parathyroid tumors. Sensitivity in finding parathyroid tumors by both imaging modalities is reportedly 80–90% according to previous reports (21, 26). Although the present patient showed severe cystic osteofibrosis of the whole body and US and MRI clearly demonstrated the parathyroid tumor, neither nuclear medicine technique detected the tumor. To rule out an ectopic PTH producing tumor and to ensure surgical
To resect the parathyroid mass, we had to perform selective venous sampling around the parathyroid and the patient was diagnosed as PHPT. Previous studies have reported a correlation between tumor size and detectability of parathyroid adenomas by Tc-99m MIBI parathyroid imaging (27, 28). However, false-negative results have been reported in large tumors, while some very small tumors have been detected. In fact, the parathyroid tumor in the present case was 2 cm in diameter and was not a small tumor. On the basis of the chemical structure of Tc-99m MIBI, it has been suggested that P-glycoprotein (P-gp) expression is involved in the transport of Tc-99m MIBI. P-gp is a plasma-membrane lipoprotein encoded by human multidrug resistance (MDR) gene. It is thought that P-gp is a drug efflux pump utilizing energy from the ATP hydrolysis to transport substrates out of the cell (29). Some recent studies have described rapid Tc-99m MIBI washout in malignant cells with high levels of P-gp. Sun et al showed that significant P-gp expression limited the sensitivity of Tc-99m MIBI parathyroid imaging to localize parathyroid adenomas before surgery (30). However, in this case, immunohistochemistry revealed that the parathyroid tumor did not express P-gp, suggesting that P-gp is not a sole explanation for the false-negative results of Tc-99m MIBI scans. Few reports describe the usefulness of FDG-PET for imaging hyperparathyroidism and they are...

**Figure 3.** $^{99m}$Tc-MIBI scintigraphy and FDG-PET failed to detect the parathyroid tumor.

**Figure 4.** Selective venous sampling for intact PTH measurement around the parathyroid. SVC: Supra Vena Cava. IVC: Inferior Vena Cava.
discordant (21–25). In a series of seven patients with hyperparathyroidism, Melon et al demonstrated uptake of FDG only in two of nine parathyroid adenomas (23). Roelants et al reported a case of recurrent medullary thyroid cancer (MTC) and PHPT in multiple endocrine neoplasia (MEN) 2A syndrome (31). They found an abnormal uptake in MTC lymph node metastasis on both a Tc-99m MIBI scan and FDG-PET, but only Tc-99m MIBI imaging detected parathyroid adenoma. They concluded that both tracers accumulated in the MTC lymph node metastasis due to its elevated metabolic status (31). On the other hand, Neumann et al reported that FDG-PET has 86% sensitivity for localization of abnormal parathyroid tissue (21). There is no clear explanation for this discordance. Considering the lack of P-gp expression in the parathyroid tumor in the current case, further analysis of cases, which demonstrate false-negative results with Tc-99m MIBI and/or FDG-PET should be explored in future studies.

Figure 5. A, B) H-E staining of the parathyroid tumor. The histological diagnosis was parathyroid adenoma. C) P-glycoprotein (P-gp) staining of the parathyroid tumor No expression of P-gp was found in the tumor. D) P-gp is expressed in the plasma membrane of an adrenal cortical adenoma (positive control).
References


