Sleeping Parathyroid Tumor: Rapid Hyperfunction after Removal of the Dominant Tumor


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Context: Due to frequent multiplicity of tumors in multiple endocrine neoplasia type 1, it may be difficult to decide when to stop a parathyroid exploration. A fall of intraoperative serum PTH by a certain percentage during parathyroid surgery is often used as one criterion for ending the operation.

Results: We report two patients with primary hyperparathyroidism due to multiple endocrine neoplasia type 1 who had their first parathyroidectomy at the National Institutes of Health. In both cases, two and a half glands were removed, an extensive search was done for an occult parathyroid tumor, and intraoperative PTH decreased markedly to the lower limits of normal, suggesting a successful operation. Despite this, both patients became hypercalcemic within 3 d after the operation and showed persistent primary hyperparathyroidism. Detailed findings suggest the following course: chronic hypercalcemia had caused near total suppression of PTH secretion by an undiscovered parathyroid tumor (sleeping parathyroid tumor). When the hypercalcemia decreased after surgery due to the removal of the dominant parathyroid tumor(s), the abnormal yet previously suppressed tumor rapidly began to oversecrete PTH and thus caused postoperative hypercalcemia.

Conclusions: Even a fall of the intraoperative PTH to the lower limits of the normal range cannot guarantee that removal of all parathyroid tumors has been complete in cases with multiple tumors. These findings likely reflect strikingly differing PTH secretory functions among distinct tumors in the same patient, with hypercalcemia at least from a dominant tumor suppressing PTH secretion by one or more other parathyroid tumors. (J Clin Endocrinol Metab 97: 1834–1841, 2012)
operation is met but hyperparathyroidism continued immediately after surgery is defined as a “false-positive” response.

We present two patients with primary hyperparathyroidism who underwent initial parathyroid surgery during which intraoperative PTH levels fell to the lower limits of normal, suggesting no residual overactive parathyroid tissue. However, primary hyperparathyroidism resumed in the days immediately after surgery, indicating a false-positive response during IPM. This raises doubts about the commonly used intraoperative criterion for surgical success, and it points to the possibility of diversity of secretory function between separate tumors in an individual patient.

**Patients and Methods**

We reviewed the medical records of all patients who had parathyroidectomy at the National Institutes of Health from January 2005 to January 2011; 80 patients with primary hyperparathyroidism had initial parathyroidectomy and IPM. Diagnoses were assigned from preoperative, intraoperative, and pathology records. There were 30 patients with multiple endocrine neoplasia type 1 (MEN1), five cases of familial isolated hyperparathyroidism, 40 patients with single adenoma, one case with double adenoma, one case of parathyroid carcinoma, and three cases with sporadic multigland disease. Although we have no fixed policy of use or omission of IPM at initial surgery in MEN1 in our institution, it has been applied to our 30 most recent cases of initial parathyroidectomy according to our research protocol. We observed a false-positive IPM only among the two cases with MEN1 that we present here. All the patients with MEN1 underwent various noninvasive imaging studies before initial parathyroidectomy as part of the research protocol. All patients signed an informed consent that was approved by the National Institutes of Health Clinical Pathology Laboratory.

During the period of this study (January 2005 to January 2011), three different immunoasays were used for intraoperative and regular PTH. All PTH assays had within-run coefficients of variation of less than 10%. Values in this manuscript are those reported by the National Institutes of Health Clinical Pathology Laboratory.

Case series in the literature that reported false positive rates separately for single gland adenoma, multigland adenoma and double adenoma were reviewed. Mean false positive rates were calculated and Fisher’s exact frequency test was used to compare the groups.

**Results**

**Case 1**

A 15-yr-old male with familial MEN1 was evaluated for primary hyperparathyroidism and nephrocalcinosis. Serum calcium was 2.91 (reference range: 2.05–2.50) mmol/liter, ionized calcium was 1.71 (reference range: 1.17–1.31) mmol/liter, and PTH was 69 pg/ml (reference range for winter: 12–52 pg/ml). The 24-h urine calcium was 6.0 (reference range: 1.25–7.50) mmol/24 h. Kidney ultrasound revealed mild right kidney hydronephrosis without a stone. A sestamibi scan of the neck showed one area of increased uptake near the lower pole of the right thyroid lobe. A parathyroid ultrasound supported the sestamibi scan.

The patient underwent parathyroidectomy (two and one half glands resection) and transcervical thymectomy. During the surgery, an enlarged and hypercellular right superior gland (1.8 × 1.4 × 1.2 cm) and left inferior gland (0.8 × 0.8 × 0.8 cm) (the latter within the cervical horn of the thymus) were resected. The left superior parathyroid was small, was partially removed, and was confirmed by biopsy to be normal parathyroid tissue, and it was marked with two clips. The right inferior gland could not be identified despite an extensive operation to appropriate locations lasting 4 h, but IPM suggested a successful operation (Fig. 1). At 10 min after resection of the largest tumor, PTH had dropped from 84 to 11 pg/ml (87% fall from baseline).

Despite an 87% fall of PTH during IPM, the patient continued to have primary hyperparathyroidism with hypercalcemia that resumed within 2 d of surgery, and he subsequently suffered from further recurrent symptomatic nephrolithiasis. Before the second operation, his kidney ultrasound showed nephrocalcinosis and a small right kidney stone but no hydronephrosis; serum calcium was 2.77 mmol/liter, and serum PTH was 76 (reference range: 16–87) pg/ml. At reoperation 2 yr after the first surgery, a hypercellular, enlarged (6 × 4 × 9 mm) left superior parathyroid gland (presumed to be enlargement from the previously marked small gland) was resected. The right inferior parathyroid gland again could not be located. Once again, IPM was a false positive and suggested a successful
operation with the intraoperative PTH decrease from 74 to 23 pg/ml at 10 min after tumor resection (~70% fall from baseline).

During the next 2 yr, the patient continued to have primary hyperparathyroidism with hypercalciuria and recurrent nephrolithiasis. His dual-energy x-ray absorptiometry scan showed osteopenia. Two years after his second operation, serum calcium was 2.55 mmol/liter, and PTH was 64 pg/ml before the last (third) surgery. He had mutually supportive preoperative ultrasound, computed tomography (CT), and magnetic resonance imaging and underwent a third operation with removal of a 0.7 × 0.4 × 0.3-cm hypercellular right inferior parathyroid gland. The gland was encased in scar tissue posterior to the right thyroid lobe. Because IPM suggested no residual parathyroid tumor (IPM showed a decrease from 122 to 16 pg/ml, or a fall of 87%), he received a fresh parathyroid autograft in the left forearm. His serum ionized calcium was 1.15 mmol/liter, and PTH was 8 pg/ml on postoperative d 1. The patient discontinued his calcium and vitamin D analogs 7 months after the last surgery. At 8 months and then at 1 yr (most recent follow-up), his serum calcium was 2.25 and 2.17 mmol/liter, and serum PTH was 29 and 29 pg/ml, respectively.

Case 2
This 21-yr-old male had familial MEN1 with a prolactinoma greater than 1 cm and primary hyperparathyroidism with a PTH level of 164 (reference range for summer: 7–32) pg/ml, ionized calcium of 1.62 mmol/liter, and 24-h urine calcium of 5.7 mmol/24 h. Dual-energy x-ray absorptiometry scan revealed osteoporosis. Parathyroid gland imaging with sestamibi scan, ultrasound, and CT all indicated the same lesion on the left side of the neck with an estimated size of 2.2 × 2.2 cm. He underwent a subtotal parathyroidectomy and transcervical thymectomy. Left inferior (1.0 × 0.6 × 0.2 cm) and left superior (1.8 × 1.5 × 1.0 cm) parathyroid tumors were removed. A small hypercellular parathyroid gland was also found and resected in the left portion of the thymus in the neck. The left inferior gland was hypercellular; however, the left superior gland was found to be normocellular. During this surgery, no definitive right superior gland was identified; however, what appeared to be an enlarged (about 2 cm) right inferior gland was mostly resected, leaving behind a small remnant marked with a clip. IPM suggested a successful operation (Fig. 1). At 5 min after removal of the largest tumor, PTH had fallen from 87 to 13 pg/ml and to 7 pg/ml (>90% fall from baseline) 10 min after removal of all tumors.

The patient continued to have hypercalcemia (2.74 mmol/liter) with a PTH of 82 (16–87) pg/ml, and his osteoporosis did not improve. Two years, later his anteroposterior spine Z score was −3.0 and 1/3 forearm Z-score was −2.6, almost exactly the same (although it was not measured with the same machine) as before the first surgery. The sestamibi scan, CT, and magnetic resonance imaging all supported the same lesion in the right retropharyngeal region. At reoperation, a hypercellular, enlarged parathyroid tumor (2.3 × 1.3 × 0.6 cm) was resected from the right retropharyngeal space (not in scar tissue), representing an undescended right superior gland. Intraoperatively his PTH decreased from 84 to 16 pg/ml (about 80% fall from baseline) 10 min after the resection of the adenoma. IPM and his course over several days suggested a successful operation (data not shown). He was discharged with calcium and calcitriol supplements. After 6 wk, he was withdrawn from calcium and vitamin D analogs, and he has had normal calcium and PTH levels throughout the subsequent 4 yr.

Both cases were followed at a distance during the interim periods between the surgeries. The data at other time points were too weak to allow a comparison of steady-state levels of calcium or PTH at times before the first operation to those data at times during the intervening period between the operations or before the last operation.

Discussion

A false-positive IPM reading
We report two patients with familial MEN1 who underwent initial surgery for primary hyperparathyroidism and had a complicated but very similar perioperative course. Both patients had bilateral neck exploration, removal of one large parathyroid tumor, and removal of all or part of two other glands along with thymectomy in their first surgeries. Each case underwent intraoperative ultrasound of the thyroid and the cervical tissues; exploration to the tracheoesophageal areas, carotid sheath; and IPM. A successful operation was suggested by a fall of PTH to the lower limits of normal after removal of enlarged glands in each case (5, 6). In both cases, IPM was falsely positive, misleading the surgeon to terminate surgery without removing all parathyroid tumor tissue. The residual parathyroid tissue caused hyperparathyroidism soon after the operation. These data provide clear support for the interpretations in our discussion.

Both cases had subsequent reexploration and remission of hyperparathyroidism after removal of other abnormal gland(s) likely responsible for the initially problematic course. The indications for reoperation were nephrolithiasis for the first case and osteoporosis for the second case (7). Furthermore, each had the same degree of high PTH
and high calcium as before their first operation. We did not observe false-positive IPM in our other five cases of familial isolated hyperparathyroidism or three cases with sporadic multigland disease. This rate of false-positive IPM is in general agreement with prior findings of rates of false-positive IPM in multigland disease vs. in single adenoma (Tables 1–3). We speculate that our false-positive finding of IPM only in MEN1 represents a bias of case numbers. Our endocrinologists have well-known experience and interest in MEN1 (8). It seems possible that the same process might occur with any cause of multiple parathyroid tumors. The purpose of this manuscript is to emphasize and discuss specifically the intraoperative and immediate postoperative dynamics of PTH and calcium and the possibility of awakening a sleeping tumor in multigland disease.

### Frequencies of misleading or false-positive readings from intraoperative PTH

We tabulated reports of IPM (persistent hyperparathyroidism despite large fall in intraoperative PTH) in patients with single adenoma, multigland disease, and double adenoma (Tables 1–3). All previous studies showed excellent predictions of surgical success (true positives) in cases of single adenoma (Table 1; mean false-positive rate, 0.4%). However, the rates of false-positive IPM were much higher in cases with multiglandular disease (Table 2; more than two affected glands; mean false-positive rate, 47%) or with double adenoma (Table 3; mean false-positive rate, 47%). There are limited reports of IPM in multigland disease in the setting of MEN1. False-positive rates in reports of MEN1-related hyperparathyroidism cases

### Table 1. Published false-positive rates for IPM in patients with a single parathyroid adenoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Total no. of patients (n)</th>
<th>Patients with single adenoma (n)</th>
<th>Criterion used to predict surgical success (% fall from baseline)</th>
<th>False-positives, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaskowiak, 2002 (34)</td>
<td>57</td>
<td>50</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Carnerio-Pla, 2006 (35)</td>
<td>516</td>
<td>494</td>
<td>50%</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Emmolo, 2005 (36)</td>
<td>125</td>
<td>105</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Clerici, 2004 (37)</td>
<td>69</td>
<td>55</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stratman, 2002 (38)</td>
<td>63</td>
<td>49</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vignalli, 2002 (39)</td>
<td>206</td>
<td>198</td>
<td>50%</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Sugg, 2004 (40)</td>
<td>233</td>
<td>204</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Westerdalh, 2004 (41)</td>
<td>103</td>
<td>90</td>
<td>60%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Barczynski, 2007 (42)</td>
<td>115</td>
<td>104</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bergson, 2004 (43)</td>
<td>376</td>
<td>325</td>
<td>50%</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Lew and Irvin, 2009 (44)</td>
<td>164</td>
<td>157</td>
<td>50%</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Ayman, 2007 (45)</td>
<td>58</td>
<td>51</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chen, 2005 (46)</td>
<td>254</td>
<td>206</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lombardi, 2008 (47)</td>
<td>207</td>
<td>197</td>
<td>50%</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Miura, 2002 (48)</td>
<td>115</td>
<td>88</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Riss, 2009 (49)</td>
<td>310</td>
<td>289</td>
<td>50% and normal range</td>
<td>7 (2.4%)</td>
</tr>
</tbody>
</table>

*Although some authors are represented in more than one table, each table has its own unique tumor category. Average false-positive rate, 0.4 ± 0.7%.

### Table 2. Published false-positive rates for IPM in patients with multigland disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Total no. of patients (n)</th>
<th>Patients with multigland disease (n)</th>
<th>Criterion used to predict surgical success (% fall from baseline)</th>
<th>False-positives, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes, 2011 (50)</td>
<td>207</td>
<td>207</td>
<td>50%</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>Richards, 2007 (51)</td>
<td>1,106</td>
<td>165</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cayo, 2009 (52)</td>
<td>755</td>
<td>163</td>
<td>50%</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ozimek, 2010 (53)</td>
<td>235</td>
<td>8</td>
<td>50% and then normal range</td>
<td>1 (12%)</td>
</tr>
<tr>
<td>Lew, 2010 (54)</td>
<td>723</td>
<td>38</td>
<td>50%</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Weber, 2004 (55)</td>
<td>45</td>
<td>45</td>
<td>50%</td>
<td>9 (20%)</td>
</tr>
<tr>
<td>Gordon, 1999 (56)</td>
<td>72</td>
<td>17</td>
<td>50%</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Carnerio-Pla, 2006 (57)</td>
<td>402</td>
<td>18</td>
<td>50%</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Sugg, 2004 (40)</td>
<td>233</td>
<td>18</td>
<td>50%</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Clerici, 2004 (37)</td>
<td>69</td>
<td>14</td>
<td>50%</td>
<td>6 (42%)</td>
</tr>
<tr>
<td>Garner and Light, 1999 (16)</td>
<td>130</td>
<td>5</td>
<td>50%</td>
<td>3 (60%)</td>
</tr>
</tbody>
</table>

*Two large series represent outliers in reporting zero false-positive rates; we included them for the purpose of completeness. They do not change the overall impressions. The average false-positive rate is higher than with single adenoma (Table 1) (P < 0.001) (Fisher’s exact test).

*Although some authors are represented in more than one table, each table has its own unique tumor category.

*Average false-positive rate, 47 ± 23%.
seem to be similar to rates in other series of multigland disease (9–14).

The predictive success of IPM has varied considerably, and it depends in part on the criteria used. There have been suggestions to use more stringent criteria to lower the frequency of false-positives. In one large study, a change in the intraoperative PTH cutoff criterion from 50 to 80% fall from baseline caused a decrease in the false-positive rate from 26 to 12% (15). In multigland parathyroid disease, an enlarged gland may not be hypersecreting. In an analysis of IPM in 130 patients, surgery was not terminated in three patients with multigland disease despite a positive intraoperative PTH test, and other enlarged glands were subsequently found and removed (16). The authors discussed that gland enlargement may not equate to hypersecretion of PTH only by that gland. It seems possible that hypercalcemia from a dominant gland causes temporary suppression of PTH secretion or has a different set point (17). We do not know the real frequency of similar courses. Among all accumulated false-positives from IPM, unknown numbers of cases with a course like that in our two may have been seen but not reported previously, and even more may have been encountered but not recognized.

**Discordant function of the tumors within one case**

Based on clinical information, the concept of different secretory and growth patterns of separate tumors in one individual case is not new. An example is the occurrence of tumors in one case of MEN1 that oversecrete completely different hormones (18). Parathyroid tumors of a different size and growth pattern may occur in one individual case (5). An extreme example is the occurrence of parathyroid cancer in one gland vs. parathyroid adenoma or hyperplasia in another gland in a case with the hyperparathyroidism-jaw tumor syndrome (19) and very rarely in a case with MEN1 (20).

Two tumors with differing secretory function seem likely to have differences in molecular or genetic disturbance. We offer several speculations about possible molecular or genetic disturbances:

**At the molecular level**

Separate parathyroid tumors in an individual MEN1 patient may present with a different PTH secretory disturbance; this has been supported by analyses of PTH secretion in vitro (21–23). Each tumor is likely to be differently programmed by its unique origin from different clonal precursor cells. They could have a difference in the curve of PTH suppression by calcium. For example, the first parathyroid tumor might have constant and abnormally nonsuppressible PTH secretion at all serum calcium levels, whereas the second tumor would only be suppressed above a certain abnormal set point (24, 25). This has been shown for parathyroid adenomas compared between two cases, but it has not yet been tested extensively or reported for two tumors in one case as in MEN1 or hyperparathyroidism-jaw tumor syndrome. Concerns around an awakening tumor cannot be evaluated in vitro because the in vitro models differ too much from in vivo conditions. Alternatively, the calcium-sensing receptor, like other serpentine receptors, interacts with some proteins. Changes in the interactions with these proteins could lead to differences in expression of the calcium-sensing receptor (26).

**At the genetic level**

We speculate, as another mechanism that, although the first and second hits at the MEN1 gene may have a similar biallelic gene inactivation consequence, subsequent third and other hits might be at completely different growth genes with different consequences for the ultimate tumor (27). Parathyroid tumors could also arise by external irradiation (28, 29). About half of these patients have mul-

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**TABLE 3. Published false-positive rates for IPM in patients with double adenomas**

<table>
<thead>
<tr>
<th>First author</th>
<th>Total no. of patients (n)</th>
<th>Patients with double adenoma (n)</th>
<th>Criterion used to predict surgical success (% fall from baseline)</th>
<th>False positives, n (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitges-Serra, 2010</td>
<td>13</td>
<td>13</td>
<td>50%</td>
<td>0 (69%)</td>
</tr>
<tr>
<td>Haciyanli, 2003</td>
<td>287</td>
<td>21</td>
<td>50%</td>
<td>0 (60%)</td>
</tr>
<tr>
<td>Jaskowiak, 2002</td>
<td>57</td>
<td>4</td>
<td>50%</td>
<td>0 (50%)</td>
</tr>
<tr>
<td>Gauger, 2001</td>
<td>20</td>
<td>20</td>
<td>50%</td>
<td>0 (55%)</td>
</tr>
<tr>
<td>Emmolo, 2005</td>
<td>125</td>
<td>8</td>
<td>50%</td>
<td>0 (50%)</td>
</tr>
<tr>
<td>Kandil, 2009</td>
<td>552</td>
<td>47</td>
<td>50%</td>
<td>0 (2%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The data for double adenoma are considered less robust than those for multigland disease due to smaller number of cases and varying criteria for diagnosis. However, the average false-positive rate is significantly higher than single adenoma (Table 1) (P < 0.001). For combined double adenoma and multigland disease groups compared with single adenoma, P < 0.0001 (Fisher exact test).

<sup>b</sup> Although some authors are represented in more than one table, each table has its own unique tumor category.

<sup>c</sup> Average false-positive rate, 47 ± 23%.
mple parathyroid tumors. It seems likely, although not proven, that the different tumors would arise from hits at different growth genes.

Awakening of a sleeping tumor: temporary suppression of PTH secretion

We hypothesize that our findings were caused by a diverse function among multiple tumors, causing the sequence indicated below. In both cases, a large tumor dominated as the main cause of hypercalcemia. The degree of dominating hypercalcemia was sufficient to suppress PTH secretion by normal glands and also by at least one other tumorous gland. Within 1 or 2 d after removal of the dominant tumor, serum calcium began to fall, relieving the suppression of the other tumor(s), which then could hypersecrete PTH immediately after surgery. It is not known whether the hypercalcemic suppression of tumoral PTH secretion would extend to suppression of tumor growth.

A second alternate explanation as a cause of sleeping is temporary surgical damage to the parathyroid tumor. Although vascular compromise to an adenoma cannot be excluded as a formal possibility, it seems unlikely in our two cases. If temporary or full vascular compromise occurs when a pressure cuff around the arm blocks arterial inflow and venous return (Casanova test), complete or partial hypoparathyroidism with hypocalcemia has not been reported (30, 31). On the other hand, if a lesion had been completely devascularized by severing its pedicle, the return of function would not be observed until beyond 2–4 wk, as in the case of placing a parathyroid autograft (32, 33). Moreover, in one of our cases, the offending tumor was far posterior in the retropharyngeal space and thus remote from the initial operative field.

A third alternate mechanism is an intraoperative shut-down of PTH secretion that continues for several hours. This phenomenon has not been noted in thousands of operations on solitary adenoma (Table 1) and is thus not likely in the setting of multigland disease.

Lastly, an artificially elevated baseline PTH from gland trauma could be deceptive. There was no reason to suspect this in either of our cases because the baseline value during IPM was similar to the chronically elevated preoperative PTH levels.

Whatever the mechanism is for the secretary suppression of some parathyroid tumors, our findings have immediate clinical relevance. Our findings show that in patients with multiple parathyroid tumors, the results of IPM should be interpreted with caution because even a fall of intraoperative PTH to the lower limits of the normal range cannot guarantee a successful operation. Our study does not address the question of whether IPM should be performed at all initial operations with MEN1. IPM can be a good adjunct study in parathyroid surgery and may be especially useful in the minimally invasive approach. However, in cases with multigland disease, as in MEN1, IPM results alone should not be the only criterion to terminate the surgery if all the parathyroid glands have not been identified.

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References
