Seigo Tachibana¹, Shinya Sato³, Tadao Yokoi³, Ryoko Nagaishi⁴, Yuko Akehi⁴, Toshihiko Yanase³ and Hiroyuki Yamashita²

Abstract

We herein report a case of severe postsurgical hypocalcemia associated with primary hyperparathyroidism (pHPT), Graves’ disease (GD) and acromegaly (AC). A 54-year-old woman was referred to our clinic for treatment of pHPT and GD. She also had active AC and was clinically diagnosed as multiple endocrine neoplasm type 1 because of pHPT and AC. Two enlarged parathyroid glands were detected by preoperative examinations. We performed total parathyroidectomy and thyroidectomy. After the operation, she showed severe hypocalcemia induced by postsurgical hypoparathyroidism and hungry bone syndrome. This is a rare case of postsurgical severe hypocalcemia associated with pHPT, GD and AC.

Key words: postsurgical hypocalcemia, hungry bone syndrome, primary hyperparathyroidism, Graves’ disease, acromegaly, MEN 1


Introduction

Postsurgical hypoparathyroidism is one of the common postsurgical complications following thyroidectomy and/or parathyroidectomy. However, in general, it is not so difficult to control the serum calcium concentration by oral administration of vitamin D3, calcium and/or venous infusion of calcium gluconate hydrate. In contrast, severe primary hyperparathyroidism (pHPT) and/or severe Graves’ disease (GD) show hyper bone turnover, often causing hungry bone syndrome. In these cases, after surgical treatment for hyperthyroidism and hyperparathyroidism the bone metabolism is dramatically changed because of decreased bone resorption and increased bone formation. If hungry bone syndrome is complicated by postsurgical hypoparathyroidism, hypocalcemia after surgery is exacerbated.

Acromegaly (AC) is often associated with pHPT in multiple endocrine neoplasm type 1 (MEN 1). It is well known that active AC patients show a metabolic disorder of the bone induced by excess growth hormone (1). Therefore, in MEN 1 patients who have both pHPT and AC, increased bone turnover due to excess growth hormone (GH) can affect postsurgical hypocalcemia after parathyroidectomy. To our knowledge, there is no report of postsurgical severe hypocalcemia in patients with pHPT, AC, and GD.

In this paper, we report a case of severe postsurgical hypocalcemia due to postsurgical hypoparathyroidism and hungry bone syndrome associated with the above-mentioned three endocrinopathies, and discuss the complicated calcium and bone metabolism of this patient in the pre- and post-operation periods.

Case Report

A 54-year-old woman presented with general fatigue, ac-
romegalic features, diffuse goiter, and mild proptosis at our clinic. About 1.5 months before she visited our clinic, she had caught a cold and visited her family doctor, who detected diffuse goiter. Then, she was introduced to an endocrinologist. She was diagnosed as GD because of high serum thyroid hormone and decreased thyroid stimulating hormone (TSH) levels with a high TSH receptor antibody titer (TRAb). After diagnosis of GD, methimazole was administered and her thyroid function was corrected gradually. In addition, AC and pHPT were also suspected because of clinical features of AC and hypercalcemia. Her GH and insulin-like growth factor 1 (IGF-1) levels were higher than the normal range, and GH was not suppressed by a 75 g oral glucose tolerance test. A micro pituitary adenoma was detected by enhanced pituitary magnetic resonance imaging. Therefore, she was diagnosed as AC. In spite of hypercalcemia, her intact parathyroid hormone (PTH) was not suppressed, and her urine calcium/creatinine excretion rate was 1.18%. Multiple regions of parathyroid swelling were suspected by neck ultrasonography (US) and computed tomography (CT). Therefore, she was diagnosed as pHPT. She was referred to the university hospital for AC treatment. After further preoperative examinations, she was introduced to our clinic for surgical treatment of pHPT before excision of the pituitary adenoma as she had severe osteoporosis and her pituitary adenoma was a micro adenoma, showing no invasion of the cavernous sinus and no pressure on the optic nerve.

At the first visit, she was 156.7 cm tall and weighed 39.2 kg, with a body mass index of 16.0. Her blood pressure was 124/73 mmHg and her pulse rate was 61 beats/min and regular. Her palpebral conjunctivae were not anemic, and her bulbar conjunctivae were not icteric. She had mild proptosis without Graefe’s sign or Dalrymple’s sign, and her face was acromegalic. Her thyroid gland was swollen diffusely. Her heart and breathing sounds were clear. The abdomen was flat and soft, and the liver and spleen were not palpable. There was no pretilial edema, and she had no finger tremors. All her fingers were swollen. She had a history of acute appendicitis and lumbar hernia. She had a history of smoking (1 pack per day), but she was not a drinker. Her family history showed paternal acute myocardial infarction and a brother’s prostate cancer. There was no history of endocrine disorder associated with MEN 1.

Her laboratory data are shown in Table 1. As shown in Table 1, her thyroid function was corrected to subclinical hyperthyroidism, but this improved thyroid function was maintained within only few weeks. Neck US showed an enlarged right lower parathyroid gland and diffuse goiter with nodular formation (Fig. 1A). Neck-enhanced CT demonstrated right lower and left lower parathyroid gland enlargement (Fig. 1B). Chest CT showed no significant findings. Abdominal CT showed bilateral renal calcification, but there were no endocrine organ tumors, including the pancreas and adrenal gland. Technetium-99 m MIBI scintigraphy did not show any suspicion of an enlarged parathyroid gland. In addition, her lumbar bone mineral density (L2-4) was 0.485 g/cm², and T-score and Z-score of her lumbar spine were -4.7 and -3.1, respectively. Her distal radius bone mineral density was 0.260 g/cm², and T-score and Z-score of her distal radius bone were -7.43 and -4.63, respectively. These data were examined by dual-energy X-ray absorptiometry (Hologic QDR-4500, USA).

Parathyroidectomy and thyroidectomy were indicated because she had severe osteoporosis and she also had GD with nodular lesions. After admission, we performed total parathyroidectomy and thyroidectomy. We resected four parathyroid glands and implanted about 50 mg of the parathyroid gland. The weights of resected parathyroid glands were 145 mg, 127 mg, 47 mg, and 18 mg, respectively. The total weight of resected thyroid glands was 36 g. The histological diagnoses were parathyroid hyperplasia and GD (Fig. 2A, 2B). On the first postoperative day, she complained of severe numbness. Her albumin corrected serum calcium concentration was 7.1 mg/dL, her phosphorus was 4.4 mg/dL, and her serum intact PTH was lower than the detection limit. Next, we administered oral alfalcacidol (3.0 μg/day), oral calcium L-aspartate hydrate (4,800 mg/day),

---

**Table 1. Laboratory Data**

<table>
<thead>
<tr>
<th>Blood count</th>
<th>WBC 9,100/μL, RBC 429 × 10^6/μL, Hb 12.0 g/dL, Hct 38.2 %, Plt 32.2 × 10^9/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood chemistry</td>
<td>TP 7.7 g/dL, Alb 4.1 g/dL, AST 17 IU/L, ALT 10 IU/L, ALP 1175 IU/L, Cre 0.3 mg/dL, T-Chol 201 mg/dL, glucose 153 mg/dL, HbA1c (JDS) 7.1 %, Na 137 mEq/L, K 4.2 mEq/L, Cl 104 mEq/L, Ca 10.3mg/dL, IP 3.3mg/dL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>sugar (-), protein (+), blood (2+), Ca 236.6 mg/day, FEca 1.18 %, %TRP 88.9%</td>
</tr>
<tr>
<td>Endocrinological findings</td>
<td>TSH 0.005 μIU/mL, free thyroxine 1.00 ng/dL, free triiodothyronine 3.82 pg/mL, TSH receptor antibody (2nd generation) 53.8 %, intact PTH 179.3 pg/mL, 1,25-(OH)₂ vitamin D 219 pg/mL, GH 7.75 ng/mL, insulin-like growth factor-1 (IGF-1) levels were higher than the normal range, and GH was not suppressed by a 75 g oral glucose tolerance test. A micro pituitary adenoma was detected by enhanced pituitary magnetic resonance imaging. Therefore, she was diagnosed as AC.</td>
</tr>
<tr>
<td>Marker of bone metabolism</td>
<td>BAP 132 IU/L, osteocalcin 36.0 ng/mL, serum NTx 41.8 nMBCE/L</td>
</tr>
</tbody>
</table>

---

1870
Figure 1. A. Right lower parathyroid enlargement (arrow) was detected by neck US and there were multiple nodular lesions in the enlarged thyroid gland. B. Not only right lower parathyroid enlargement, but also left lower parathyroid enlargement, was detected by enhanced CT. Both parathyroid enlargements are shown by arrows.

Figure 2. A. Postsurgical histological examination demonstrated parathyroid hyperplasia. The weights of resected parathyroid glands were 145 mg, 127 mg, 47 mg, and 18 mg. B. Postsurgical histological examination also demonstrated typical histological Graves’ disease changes. Enlarged follicles and epithelia were observed.

and intravenous calcium gluconate hydrate (1,700 mg/day). However, her calcium concentration did not improve, and we had to increase administered calcium gradually. Consequently, oral calcium L-aspartate hydrate was increased to 6,400 mg/day and intravenous calcium gluconate hydrate was increased to 6,800 mg/day. On the 10th day after surgery, intact PTH was detectable, and it was 5.0 pg/mL. Despite administration of high dose of calcium, her calcium concentration did not improve adequately, but her clinical manifestations improved. After interruption of intravenous calcium gluconate hydrate, her clinical manifestations did not deteriorate. Therefore, she was discharged on the 18th day after surgery. Her clinical course is shown in Fig. 3.

After discharge, she did not complain of tetany, and her calcium concentration improved gradually with administration of oral alfacalcidol and calcium L-aspartate hydrate. It required 3 months to increase the calcium concentration to over 8.0 mg/dL. Her bone mineral density recovered up to 0.645 g/cm² at 16 months after surgery. The increasing rate of bone mineral density was 33.9%/year. During this period,
she underwent transsphenoidal surgery (TSS) for AC and her IGF-1 was controlled within normal range by somatostatin after TSS. At 17 months after surgery for pHPT and GD, the bone markers were improved dramatically; serum level of bone alkaline phosphatase (BAP), osteocalcin and type I collagen cross-linked N-telopeptide (NTx) was 11.4 IU/L, 3.8 ng/mL, and 9.7 nMBCE/L, respectively.

We encountered severe hypocalcemia associated with postsurgical hypoparathyroidism and hungry bone syndrome in a patient with pHPT, GD, and AC. In general, in pHPT associated with MEN 1, total parathyroidectomy (TPTX) and autologous graft of the parathyroid tissue or subtotal parathyroidectomy are recommended because of the high recurrence rate of pHPT after removing only enlarged parathyroid gland(s) (2, 3). In the present case, we chose TPTX to avoid the recurrence of pHPT. However, after TPTX, secretion of PTH ceased, so-called complete hypoparathyroidism. It takes several weeks to restore parathyroid function of a parathyroid tissue autologous graft. Therefore, the duration of postsurgical hypoparathyroidism after total parathyroidectomy for patients with parathyroid hyperplasia is longer than that for patients with parathyroid adenoma (4). We considered that this was one of the main causes of severe postsurgical hypocalcemia in this patient. In addition, on the first day after surgery, serum phosphorus was not increased, indicating that hungry bone syndrome also influenced her calcium metabolism.

It is well known that various endocrinopathies affect bone metabolism (1). In pHPT and GD, bone turnover is increased, showing increased bone resorption and bone formation (5-7). Before treatment, bone resorption is greater than bone formation, causing osteoporosis. After treatment, particularly parathyroidectomy or thyroidectomy, the bone metabolism changes immediately because of not only postsurgical hypoparathyroidism, but also immediate correction of hyperparathyroidism or hyperthyroidism. In brief, bone formation becomes greater than bone resorption after surgery, resulting in increased demand for calcium. In fact, there

Figure 3. The Clinical Course after Surgery. Alfacalcidol and Ca L-aspartate Hydrate were Administered Orally

Table 2. A Summary of How Calcium Metabolism was Affected by PHPT, GD, and AC

<table>
<thead>
<tr>
<th>Bone Metabolism</th>
<th>Ca (mg/dL)</th>
<th>IP (mg/dL)</th>
<th>intact PTH</th>
<th>bone resorption</th>
<th>bone formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>pHPT (pre)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>pHPT (post)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>GD (pre)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>GD (post)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>AC (pre)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>AC (post)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

The calcium metabolism before TPTX and total thyroidectomy is shown in the ‘pre’ line. The calcium metabolism after TPTX and total thyroidectomy is shown in the ‘post’ line. In calcium metabolism associated with pHPT, after TPTX Ca and intact PTH decreased and IP increased because of postsurgical hypoparathyroidism. In addition, bone formation was greater than bone resorption because of the hyperparathyroidism correction. Calcium metabolism associated with GD often shows various states depending on thyroid function after medication. In this case, her thyroid function before total thyroidectomy was still subclinical hyperthyroidism. Therefore, bone resorption was still greater than bone formation. After total thyroidectomy, Ca, IP, and intact PTH are shown in Table 2 because of postsurgical hypoparathyroidism and/or secondary hyperparathyroidism due to increased demand for calcium. In addition, bone formation was greater than bone resorption because of the hyperparathyroidism correction. The calcium metabolism associated with AC after TPTX and total thyroidectomy did not change because these procedures did not influence excess growth hormone secretion.

Discussion

We encountered severe hypocalcemia associated with postsurgical hypoparathyroidism and hungry bone syndrome in a patient with pHPT, GD, and AC. In general, in pHPT associated with MEN 1, total parathyroidectomy (TPTX) and autologous graft of the parathyroid tissue or subtotal parathyroidectomy are recommended because of the high recurrence rate of pHPT after removing only enlarged parathyroid gland(s) (2, 3). In the present case, we chose TPTX to avoid the recurrence of pHPT. However, after TPTX, secretion of PTH ceased, so-called complete hypoparathyroidism. It takes several weeks to restore parathyroid function of a parathyroid tissue autologous graft. Therefore, the duration of postsurgical hypoparathyroidism after total parathyroidectomy for patients with parathyroid hyperplasia is longer than that for patients with parathyroid adenoma (4). We considered that this was one of the main causes of severe postsurgical hypocalcemia in this patient. In addition, on the first day after surgery, serum phosphorus was not increased, indicating that hungry bone syndrome also influenced her calcium metabolism.

It is well known that various endocrinopathies affect bone metabolism (1). In pHPT and GD, bone turnover is increased, showing increased bone resorption and bone formation (5-7). Before treatment, bone resorption is greater than bone formation, causing osteoporosis. After treatment, particularly parathyroidectomy or thyroidectomy, the bone metabolism changes immediately because of not only postsurgical hypoparathyroidism, but also immediate correction of hyperparathyroidism or hyperthyroidism. In brief, bone formation becomes greater than bone resorption after surgery, resulting in increased demand for calcium. In fact, there
have been some reports of hungry bone syndrome or osteoporosis associated with pHPT (8, 9). In addition, Yamashita et al. reported that GD patients often show secondary hyperparathyroidism because of a relative deficiency in calcium and vitamin D due to increased demand for bone restoration after preoperative medical therapy (10). Therefore, in the present case, we thought that both pHPT and GD affected postoperative hungry bone syndrome.

AC could also contribute to postsurgical hypocalcemia. In active AC patients, biochemical markers of bone formation and bone resorption are increased, but markers of bone resorption are disproportionately increased in relation to those of bone formation (11). In fact, in the present case, the markers of bone resorption and bone formation were very high. After the treatment for AC, the markers of bone metabolism were dramatically improved to normal range. It was difficult to evaluate the bone metabolic effect of the treatment for AC, because the data of bone metabolic markers after the treatment for pHPT and GD with AC were not available. However, in reviewing the literature on AC and bone metabolism, these results may indicate that not only pHPT and GD, but also AC, influenced her bone metabolism. We concluded that disproportionate increased bone resorption compared to increased bone formation due to excess growth hormone might contribute to preoperative bone loss and postoperative hungry bone syndrome. On the other hand, after TPTX, we also considered that GH excess might contribute to the prevention of severe hypocalcemia because of the increase of calcium efflux to circulation stimulated by GH excess. The present case showed very complex bone and calcium metabolism influenced by multiple endocrinopathies including pHPT, GD, and AC and these are summarized in Table 2. To our knowledge, there is no report of GD associated with MEN 1. As far as the etiology of MEN 1 is concerned, GD seemed to be unrelated to MEN 1, because MEN 1 is an endocrine disorder due to endocrine neoplasm associated with MEN 1 gene mutation. However, this accidental concomitance was considered to be one of the important roles of the above-mentioned complex bone and calcium metabolism.

In conclusion, we report a case with severe hypocalcemia after total parathyroidectomy and thyroidectomy in a MEN 1 patient with pHPT, GD and AC. Severe hypocalcemia resulted from hypoparathyroidism and hungry bone syndrome induced by three endocrinopathies which increased bone resorption, resulting in severe bone loss.

The authors state that they have no Conflict of Interest (COI).

References