Case Report

Lessons learned from the management of Hungry Bone Syndrome following the removal of an Atypical Parathyroid Adenoma

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Abstract

Hungry Bone Syndrome (HBS) refers to rapid, profound, and prolonged hypocalcemia associated with hypophosphatemia and hypomagnesemia occurring in patients with increased bone turnover after successful management of the underlying disorder. We describe a male patient with primary hyperparathyroidism (PHPT), in whom HBS was diagnosed 6 months after parathyroidectomy. Histopathologic examination revealed an atypical parathyroid adenoma (APA), while immunohistochemistry showed cell proliferation index Ki-67 10% and overexpression of cyclin D1 (>90%). Preoperative treatment with vitamin D3 had normalized 25OHD and alkaline phosphatase levels, reflected in an improvement in bone turnover prior to surgery. Postoperative treatment for HBS with alfacalcidol, calcium, vitamin D3 and magnesium was administered for a long period. This treatment prevented severe postoperative hypocalcemia and he was discharged two days later. Preoperative cinacalcet treatment did not reduce hypercalcemia implying that the tumor had lack of calcium-sensing receptors (CaSR). In conclusion, preoperative restoration of low 25OHD levels is essential for prevention of HBS. Postoperative treatment with active metabolites of vitamin D must be initiated as early as possible, in order to prevent or minimize the development of HBS, and to reduce the duration of hospitalization.

Keywords: Hungry Bone Syndrome, Atypical Parathyroid Adenoma, Ki-67 Index, Vitamin D3, Alfacalcidol

Introduction

Hungry Bone Syndrome (HBS) is usually a complication of successful parathyroidectomy for severe primary hyperparathyroidism (PHPT) which is associated with preoperative high bone turnover. HBS is characterized by profound and prolonged hypocalcemia and hypomagnesemia. The abrupt postoperative removal of the high circulating levels of PTH results in an increased influx of calcium into the skeleton in order to meet the needs of the rebound bone formation, while bone resorption is arrested. Postoperatively, HBS is characterized by elevated PTH levels in patients with severe PHPT, whereas HBS is quite rare in patients with mild PHPT. The most common diagnoses associated with HBS are PHPT and secondary or tertiary hyperparathyroidism after parathyroidectomy, in patients with end-stage renal disease receiving renal replacement therapy or with a functioning renal transplant. Another diagnosis sometimes associated with usually a mild form of HBS is severe thyrotoxicosis associated with high bone turnover in which hypocalcaemia may occur in up to 46% of patients, while HBS may last for up to 3 months after the initiation of hyperthyroidism treatment (surgical or medical). In contrast to HBS due to PHPT, hypocalcaemia that arises following treatment for hyperthyroidism is associated with appropriate increase of PTH levels. Less frequent causes of HBS are parathyroid cancer (PC) and metastatic prostate cancer. Bone metastases from prostate cancer are predominantly osteoblastic and commonly cause increased levels of PTH as...
calcium is transferred from serum into the osteoblast-rich neoplastic environment.

Nowadays, HBS rarely involves skeletal manifestations such as brown tumors and osteitis fibrosa cystica, whereas fragility fractures due to severe osteoporosis are more likely to be occurred. HBS develops postoperatively in up to 13% of patients with PHPT, although this figure varies among centers. The duration of the syndrome has been defined as the time needed for bone remineralization and normalization of bone turnover markers, as well as the time required for normalization of serum calcium following successful parathyroidectomy. In addition, improvement or normalization of bone mineral density (BMD) is considered to be a criterion for resolution of HBS, and several studies adopting this notion have reported that HBS may last from 4.5 to 16 months. Nevertheless, there is as yet no consensus on a definition of disease duration for HBS.

We herein describe a case of PHPT without severe skeletal findings, in which HBS was diagnosed 6 months after the surgical excision of an atypical parathyroid adenoma (APA).

Table 1. Laboratory findings preoperatively (Preop) and postoperatively (Postop).

|                      | Preop | Preop cinacalcet vitamin D3 magnesium | Postop 48 h | Postop 6m vitamin D3 calcium magnesium without alfacalcidol HBS | Postop 8m alfacalcidol vitamin D3 calcium magnesium | Post 20m alendronate alfacalcidol vitamin D3 calcium magnesium | Postop 4 years without treatment | Reference values |
|----------------------|-------|---------------------------------------|-------------|---------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------|----------------------------------|------------------|
| Corrected Calcium serum | 12.26 | 12.36                                 | 8.64        | 8.06                                                          | 9.04                                              | 8.94                                                          | 8.76                                            | 8.6 - 10.2       |
| Calcium serum (mg/dL) | 12.5  | 12.6                                  | 8.8         | 8.3                                                           | 9.2                                               | 9.1                                                           | 9.0                                             | 8.6 - 10.2       |
| Albumin serum (mg/dL) | 4.3   | 4.3                                   | 4.2         | 4.3                                                           | 4.2                                               | 4.2                                                           | 4.3                                             | 3.5 - 5.5        |
| Phosphate serum (mg/dL) | 1.9   | 1.6                                   | 3.6         | 2.4                                                           | 2.7                                               | 3.2                                                           | 1.8                                             | 2.5 - 4.5        |
| Magnesium serum (mg/dL) | 1.7   |                                        | 1.8         | 1.8                                                           |                                                   | 1.8                                                           |                                                  | 1.6 - 2.6        |
| Creatinine serum (mg/dL) | 0.9   |                                        | 1.0         | 1.0                                                           |                                                   | 1.0                                                           |                                                  | 0.4 - 1.09       |
| Alkaline phosphatase (ALP) (U/L) | 1015  | 275                                   | 123         | 68                                                            | 73                                                | 50 - 290                                                      |                                                  |                  |
| 24-hour urine calcium (mg/24h) | 485   |                                        | 37          | 218                                                           | 208                                               | 100 - 300                                                     |                                                  |                  |
| 24-hour urine creatinine (mg/24h) | 1356  |                                        | 1655        | 1645                                                          | 1645                                              | 1040 - 2300                                                   |                                                  |                  |
| 25OHD (ng/mL) | 8     | 27                                    | 31          | 15.2                                                          |                                                   | > 20 ng/mL                                                    |                                                  |                  |
| 1,25 (OH)2 D (pg/mL) | 18    |                                        | 25          | 26.3                                                          | 18 - 65                                           | 15 - 65                                                       |                                                  |                  |
| PTH (pg/mL) | 1131  | 1315                                   | 34          | 120                                                           | 60                                                | 62                                                            | 102                                             | 15 - 65          |
| TSH (μUI/mL) | 1.87  |                                        | 2.6         | 0.36 - 4.94                                                  |                                                   |                                                                |                                                  |                  |

*a Corrected calcium with albumin using the following formula: calcium measured + 0.8 (4 - albumin measured).

HBS: Hungry bone syndrome.
Case presentation

A 44-year-old Caucasian male presented with a history of arthralgia and myalgia for several months. Medical history of nephrolithiasis was reported.

The initial laboratory results were as follows: corrected serum calcium 12.26 mg/dL (normal range 8.6-10.2), phosphate levels 1.9 mg/dL (normal range 2.5-4.5), magnesium levels 1.7 mg/dL (normal range 1.6-2.6) and alkaline phosphatase levels (ALP) 1015 U/L (normal range 50-290). The elevated PTH levels of 1 131 pg/mL (normal range 15-65) together with hypercalcaemia confirmed the diagnosis of PHPT, despite low levels of 25OHD and 1,25(OH)2D of 8 ng/mL (sufficiency >20) and 18 pg/mL (normal range 18-65), respectively. Hypercalciuria (485 mg/24 hours) was also found (Table 1).

Skeletal X-rays of the hip-pelvis and lumbar spine showed diffuse osteopenia without any skeletal fractures. The initial dual energy X-ray absorptiometry (DXA) scan confirmed BMD below the expected range for age10 [left neck Z-score -4.28] (Table 2). Technetium-99m-pertechnetate whole-body scan did not reveal any skeletal lesion.

Neck ultrasonography showed a hypoechoic mass measuring 2.6 x 3.6 cm with a well-defined margin posterior to the right lobe of the thyroid gland, without signs of blood flow (Figure 1a, b). 99Tc-sestamibi scintigraphy revealed persistence of the radionucleotide in the right posterior parathyroid gland, but with extension of the radionucleotide to the upper right mediastinum (Figure 1c). Therefore, neck MRI was performed and a large mass with cystic degeneration measuring 8.7 x 4.6 cm was found posterior to the right thyroid lobe extending to the right mediastinum, while shifting the trachea and the esophagus to the left (Figure 1d).

A diagnosis of PHPT due to a large parathyroid tumor was established. Preoperative treatment with cinacalcet 30 mg b.i.d. was initiated with a daily dose of 2000 IU vitamin D3 (cholecalciferol) and 243 mg of magnesium, in order to control the hypercalcaemia and correct the low levels of 250HD and magnesium, respectively. Nevertheless, corrected serum calcium levels remained increased at 12.36 mg/dL, while 250HD levels were partially corrected to 15 ng/mL. Daily doses of cinacalcet and vitamin D3 were subsequently increased to 60 mg t.i.d. and 4000 IU, respectively, resulting in correction of 250HD and ALP levels, although hypercalcaemia persisted (Table 1). Subsequently, cinacalcet treatment was ceased due to the unresolved hypercalcaemia, while the vitamin D3 daily dose was reduced to 27 ng/mL. Bisphosphonates were not used preoperatively.

Total surgical excision of the tumor was performed without any surgical complications. Postoperatively the patient had asymptomatic hypocalcaemia (corrected serum calcium 12.36 mg/dL) with inappropriately normal PTH levels of 34 pg/ml, confirming successful parathyroidectomy (Table 1).

Histopathological examination revealed a tumor weighing 22 grams and measuring 7.2 x 4.5 x 2.7 cm. The parathyroid neoplasm consisted of solid and cystic areas with fibrosis and partial capsular invasion, however, without extensive local infiltration or metastasis. Immunohistochemistry showed increased expression of cyclin D1 (>90%) and cell proliferation Ki-67 index (with MIB 1 antibody) was 10%. The tumor was classified as an APA11 (Figure 1 e, f).

Six months later, PTH levels were increased with low levels of calcium, phosphate and magnesium, and normal levels of 250HD and ALP (Table 1). The patient’s treatment included calcium carbonate/D3 tablets of 1000mg/880 IU twice per day and 243 mg of magnesium, whereas alfalcacidol had

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Table 2. Dual energy X-ray absorptiometry (DXA) values preoperatively and postoperatively.

|                      | Preoperative | Postoperative 12m a | Postoperative 36m |
|----------------------|--------------|---------------------|-------------------|
| **Left Femoral Neck**|              |                     |                   |
| BMD (g/cm²)         | 0.443        | 0.706               | 0.746             |
| Z-score             | -4.28        | -2.3                | -1.9              |
| **Right Femoral Neck**|            |                     |                   |
| BMD (g/cm²)         | n/a          | 0.773               | 0.812             |
| Z-score             | -1.8         | -1.4                |                   |
| **Lumbar L1-L4**    |              |                     |                   |
| BMD (g/cm²)         | n/a          | 1.059               | 1.116             |
| Z-score             | -1.3         | -0.8                |                   |

*Osteoporosis is diagnosed when BMD is below the expected range for age (Z-score < -2.0)*

* Treatment with alendronate was given for 1 year after postoperative DXA at 12 months*
been ceased 2 months previously. HBS was diagnosed and alfalcaldol 1mcg was recommended, with concomitant use of calcium carbonate/D3 and magnesium. PTH and calcium levels were normalized, after 2 months (Table 1).

Twelve months following parathyroidectomy, DXA showed a significant increase of 59.4% in the left femoral neck BMD (Table 2). As BMD, in the left femoral neck, was still below the expected range for age [left neck Z-score -2.3], alendronate 70 mg weekly was administered for 12 months as additional treatment together with alfalcaldol, calcium carbonate, cholecalciferol, and magnesium. Six months later, serum levels of corrected calcium, phosphate, ALP and PTH were normalized (Table 1). Three years after parathyroidectomy, a new DXA showed a further increase of BMD in all skeletal sites: lumbar spine (+5.4%); left hip (+5.7%) and of the right hip (+5.0%), indicating a positive effect of adrenonate treatment and parathyroidectomy (Table 2). It was therefore decided that no additional treatment was required.

Six months later (4 years postoperatively), PTH was once again increased to 102 pg/mL with low levels of phosphate, magnesium, and 25OHD, while corrected calcium levels were low normal at 8.76 mg/dL (Table 1).

Secondary hyperparathyroidism (sHPT) due to vitamin D deficiency seemed as the most possible diagnosis, although persistent of HBS was a less likely option, and treatment with alfalcaldol, calcium, vitamin D3 and magnesium was recommended. Additional treatment with alendronate was not considered necessary as BMD values were within the expected range for age (Table 2).

**Discussion**

Hypocalcemia following successful parathyroidectomy is usually transient, lasting less than a week, since the associated PHPT bone disease is frequently mild and the remaining normal parathyroid glands recover rapidly, even after long-term suppression by the hyperfunctioning parathyroid adenoma12,13.

In patients with PHPT and preoperative high rates of bone turnover, a successful parathyroidectomy limits osteoclastic resorption, which in turn decreases the activation frequency of new remodeling sites and remodeling space, leading to a consequent gain of bone mass. This mechanism in combination with the homeostatic increase of bone formation which corrects the PHPT-induced bone

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**Figure 1.** Neck ultrasonography (a, b): Hypoechogenic mass measuring 2.6 x 3.6 cm with well-defined margin posterior to the right lobe of the thyroid gland without signs of blood flow. 99Tc-sestamibi scintigraphy (c): Persistence of the radionuclide material in the right posterior parathyroid gland with extension of the radionuclide material in the upper right mediastinum. Neck MRI (d): A large mass with cystic degeneration measuring 8.7 x 4.6 cm posterior to the right thyroid lobe extending to the right mediastinum with trachea and esophagus shift to the left. (e): Atypical parathyroid adenoma. HE 250X. (f): Overexpression of the proliferation index Ki67 (MIB 1). Immunohistochemistry 250X.
incorporation into bone is thought to be by 14,15.
Magnesium levels after parathyroidectomy may decrease
due to increased bone mineralization, especially in
patients with PTH-related bone disease, such as osteitis
fibrosa. In our case, magnesium level was low normal
preoperatively and remained low normal postoperatively,
spite supplementation for a long period. Hypomagnesemia
in PHPT is an uncommon finding. It has been shown that few
patients with PHPT have high urinary magnesium output,
indicating a defect in renal magnesium retention.

PHPT-related bone disease, such as brown tumors or
osteitis fibrosa and skeletal fractures, is of considerable
importance for the development of HBS, as it has been reported
in 25-90% of patients with skeletal involvement compared
with 0-6% of patients without skeletal involvement. It is of
interest that our patient developed HBS without any of the
above skeletal findings or fracture. Another interesting point
is the young age of our patient, since older age at the time of
HBS diagnosis is considered as an additional risk factor for
the development of the syndrome.

Low preoperative 25OHD has been also proposed as
an important factor that increases the risk for HBS. In
PHPT, vitamin D insufficiency is more common than in the
general population. Low 25OHD levels in PHPT patients,
have been associated with greater severity of disease,
higher bone turnover and BMD reduction, more severe
postoperative hypocalcemia, and higher overall PTH levels.
A randomized study, showed that daily high-dose vitamin D
supplementation of 2800 IU for 6 months preoperatively and
6 months postoperatively is a safe way to improves vitamin D
status in PHPT patients, without increasing plasma or urinary
calcium. In addition, preoperative treatment with vitamin D3
reduced bone resorption and was followed by postoperative
reduction of PTH and ALP levels, confirming that preoperative
vitamin D3 supplementation may decrease the likelihood of
development of HBS. In our case, the preoperative vitamin
D3 treatment normalized 25OHD and ALP levels, reflecting
a possible improvement of bone turnover prior to surgery.
Treatment with alfacalcidol and calcium was initiated
immediately after parathyroidectomy, with concomitant use
of cholecalciferol and magnesium. This treatment course
prevented severe postoperative hypocalcemia, and the
patient was discharged two days later, without the need for
an intravenous calcium infusion. A case report has been
published with a patient presenting protracted and severe HBS
requiring 3 months of intravenous calcium supplementation,
whereas the patient received ergocalciferol and calcitriol,
before and after parathyroidectomy. The authors reported
that 25OHD levels never reached a value above 30 ng/
ml, despite the administration of ergocalciferol, and this
underlines the importance of 25OHD levels normalization
with cholecalciferol.

Postoperative treatment with active metabolites of
vitamin D with concomitant use of calcium and cholecalciferol
are considered mandatory and need to be initiated as early
possible in order to prevent or ameliorate HBS. Several case
reports of patients with HBS have described the difficulties
involved in the postoperative management of hypocalcemia
whenever the treatment consists solely of calcium plus
cholecalciferol (vitamin D2) or calcitriol (vitamin D3)
without concomitant use of vitamin D active metabolites.

In our case, the preoperative hypercalcemia was not
adequately controlled even with high-dose cinacalcet treatment,
this arousing speculation that the tumor lacked
expression of the calcium sensing receptor (CaSR). Cinacalcet
is a calcimimetic agent which directly lowers PTH levels by
increasing the sensitivity of the CaSR to extracellular calcium.
Immunohistochemical studies have shown that global loss of
CaSR staining in parathyroid tumors is a diagnostic marker
for PC. However, in our case study the histopathologic
diagnosis of an APA was established, because the tumor
exhibited some features of a parathyroid carcinoma such as
fibrosis and partial capsular invasion but had lack of
unequivocal invasive growth and metastasis. APA may be
considered tumor of uncertain malignant potential, and most
patients with APA have a benign clinical course.

Most of the bone loss in PHPT patients is reversible after
parathyroidectomy. In a case series of patients with HBS,
parathyroidectomy improved femoral neck BMD scores from
35% to 131% year after successful surgery. In addition,
case reports showed an increase in BMD of the lumbar spine
of 27% to 63% year after parathyroidectomy.

Preoperative treatment with bisphosphonates in HBS is
controversial. A retrospective case series of 46 patients
with severe bone disease, who were treated with zoledronate
preoperatively, showed a low frequency of postoperative
HBS of only 4%. In contrast, other case reports using
bisphosphonates prior to surgery demonstrated no such
effect. The aim of the preoperative bisphosphonate
treatment is to reduce bone turnover by inhibition of
osteoclast bone resorption, and to decrease the activation
frequency of remodeling space, thus resulting in refliling
of remodeling space and increasing mineralization of
the bone. However, short-term preoperative bisphosphonate
treatment may exacerbate postoperative hypocalcemia by
reducing bone resorption, without allowing time for a coupled
decrease in bone formation. In our case, alendronate
was given for 1 year, postoperatively, when the DXA has
showed that BMD was still below the expected range for age.

In our patient high PTH levels with low normal calcium,
phosphate, and suboptimal 25OHD levels were measured 4
years after parathyroidectomy, concomitantly with normal
BMD, ALP, and 24-hour urine calcium levels (Table 1).
Postoperative treatment included alendronate for 1 year and
cholecalciferol, alfacalcidol and magnesium for more than 3
years. Secondary hyperparathyroidism (sHPT) due to vitamin
D deficiency may be considered as the most likely diagnosis
in our case. However, in sHPT the increases of serum PTH
associated with vitamin D deficiency are usually within the
high normal reference range. In a large vitamin D study,
it was determined that the negative relationship between
serum PTH and serum 25(OH)D was significant only when serum 25(OH)D was lower than 12 ng/ml\textsuperscript{21}. Furthermore, high PTH levels occurs in only 10\% to 33\% of people with vitamin D insufficiency\textsuperscript{22}. In our case report, the high PTH levels in correlation with the lack of hypocalcemia and the normal 24-hour urine calcium levels indicate that HBS could be an alternative, less possible, diagnosis. Unfortunately, there are no available data regarding the postoperative use of bisphosphonates after parathyroidectomy, for the prevention or amelioration of HBS. However, it may be speculated that the postoperative treatment with alendronate for 1 year maintained low normal calcium levels by decreasing calcium influx to the bone, and thus masking the presentation of HBS while making SHPT the most acceptable diagnosis in our case.

**Conclusion**

Preoperative restoration of 25OHD levels is essential for prevention of HBS, though only vitamin D3 preparations are recommended, since vitamin D2 preparations have much lower efficiency in restoring vitamin D levels\textsuperscript{23}. Postoperative treatment with active metabolites of vitamin D, must be initiated as early as possible in order to prevent the development of HBS, and to reduce the duration of hospitalization. Magnesium supplementation is also important for the prevention and treatment of HBS, given that hypocalcemia is very difficult to resolve if there is concomitant hypomagnesemia. Data on the management of HBS are limited, while clinical guidelines and consensus regarding the precise definition and management of the syndrome are as yet lacking.

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