

## Case Report

# Successful cinacalcet treatment of refractory secondary hyperparathyroidism due to multiple lung parathyroid adenomas

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### Abstract

We describe a 56-year-old woman who presented with end-stage renal disease due to pregnancy-induced hypertension and secondary hyperparathyroidism (sHPT). She had started hemodialysis and underwent a subtotal parathyroidectomy (PTx). However, intact parathyroid hormone (iPTH) levels increased gradually. Eventually, she underwent a second PTx. However, therapy failed to significantly decrease iPTH levels. A third PTx was performed, but no pathological parathyroid tissue was found. Computed tomography scan indicated the presence of multiple ectopic lung nodules and 26 nodules were surgically removed from the left lung. Despite surgical treatment, iPTH levels remained high. Additional maxacalcitol failed to decrease iPTH levels, cinacalcet was then started. iPTH levels decreased and the cinacalcet dose could be reduced to maintenance doses of 60 mg/day. Throughout the 1.6 years of treatment, serum iPTH, alkaline phosphatase (ALP) and bone alkaline phosphatase (BAP) were normalized. As a consequence, bone pain gradually disappeared. Bone mineral density (BMD) was improved by administration of cinacalcet. In conclusion, cinacalcet was effective in this patient with refractory and inoperable sHPT. In addition, it improves their BMD and relieves bone pain.

**Keywords:** cinacalcet; haemodialysis; hyperparathyroidism; ectopic parathyroid adenoma

### Introduction

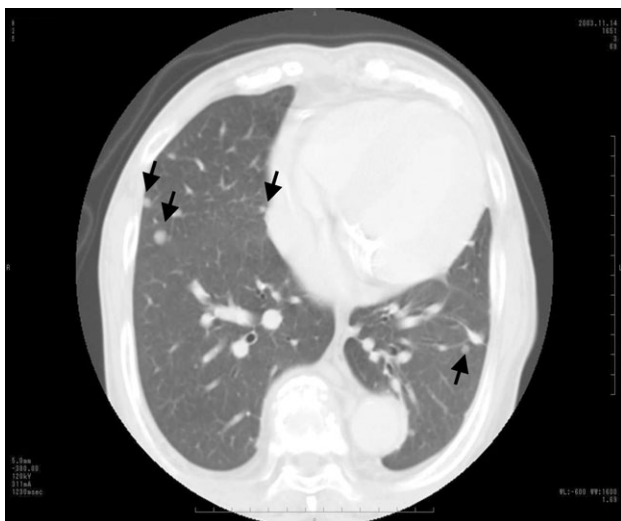
Progressive and refractory secondary hyperparathyroidism (sHPT) is a serious complication of end-stage renal disease (ESRD) accompanied by cellular transformation of the parathyroids, which often results in aggressive growth of the glands and decreased expression of both vitamin D and calcium-sensing receptors (CaSR) on their surfaces [1]. Vitamin D and phosphate binders are widely used to prevent the progression of sHPT. However, these conventional treatments often fail to control severe sHPT. In such cases, parathyroidectomy (PTx) is required. However, the frequent

growth of sHPT tumours occurring outside the neck, e.g. in the lungs, is not always treated surgically [2]. Herein, we describe successful treatment with cinacalcet of refractory sHPT due to multiple lung parathyroid adenomas.

### Case report

A 56-year-old woman was referred to our hospital in October 2003 with a diagnosis of ESRD due to pregnancy-induced hypertension and sHPT. According to her medical records, she had started haemodialysis in March 1994 and underwent a subtotal PTx in the same year. During surgery, a parathyroid adenoma involving the right lower and left lower parathyroid glands was removed, and PTx was successful. A gradual increase in intact parathyroid hormone (iPTH) levels was, however, observed 6 years later. Eventually, in February 2001, she underwent a second PTx. The two evidently enlarged parathyroid glands (each 5 × 10 mm in size) were removed. Nodules were well circumscribed, solid and yellow–white in colour. Histological examination showed parathyroid adenomas with oxyphilic cytoplasm but neither necrosis nor vascular invasion. There was no histopathological evidence of malignancy. However, therapy failed to significantly decrease iPTH levels, which ranged from 1500–2000 pg/mL. A third PTx was performed, but no pathological parathyroid tissue was found.

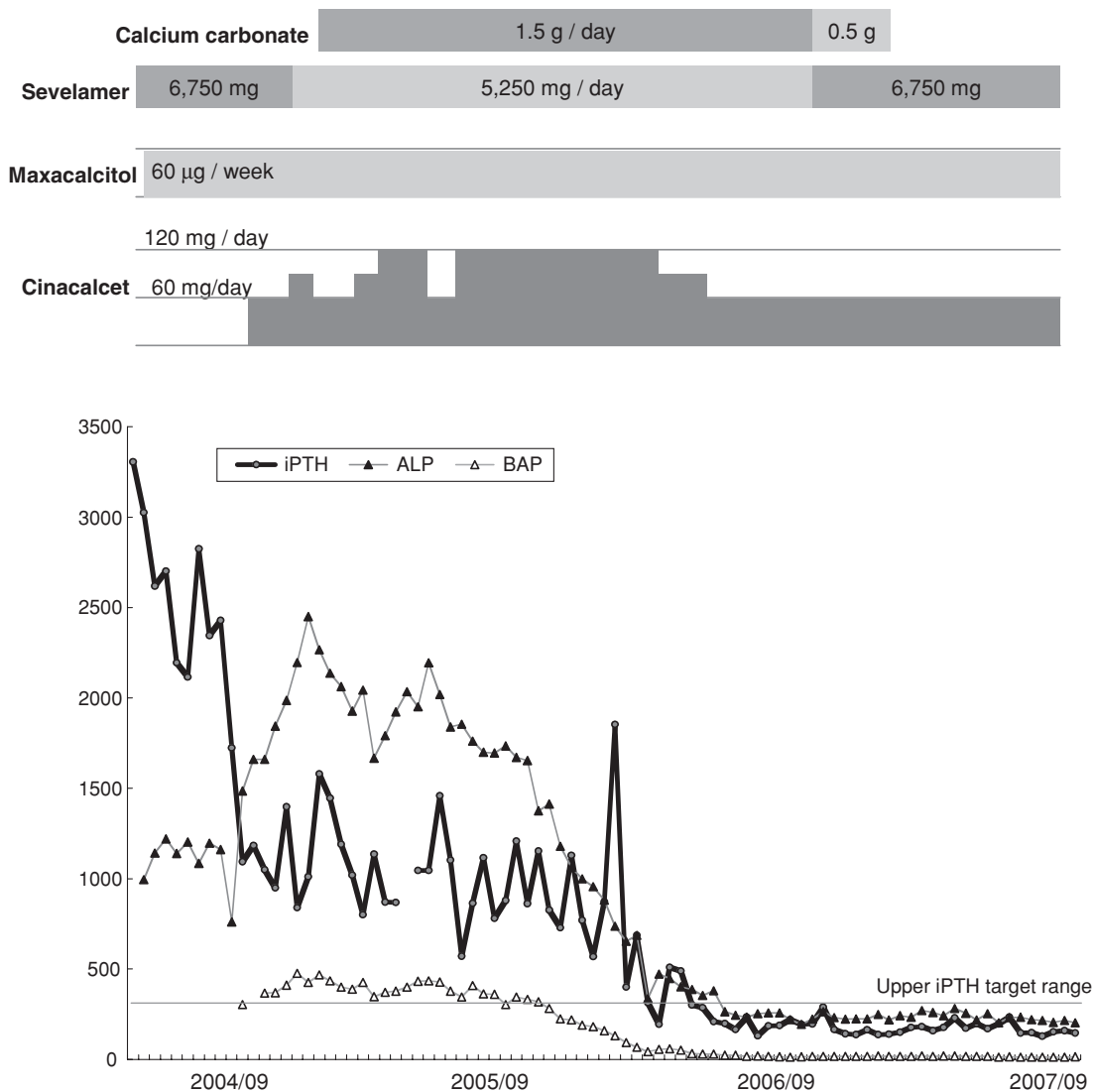
In July 2002, a computed tomography (CT) scan indicated the presence of multiple ectopic lung nodules. In September 2002, 26 nodules were surgically removed from the left lung. Intraoperative histological examination showed parathyroid adenoma. Despite surgical treatment, iPTH levels remained high. In addition, maxacalcitol was administered intravenously at a dose of 20 µg after each dialysis session. Nevertheless, iPTH levels kept increasing, and were in the 2000–4000 pg/mL range. She mainly complained of worsening bone pain and loss of height (from 162–154 cm). In October 2003, we identified the right mediastinal parathyroid glands by MIBI (99mTc-sesta-MIBI) scintigraphy. In November 2003, CT scan detected the presence of multiple ectopic nodules mainly in the right lung (Figure 1). She declined further surgical treatment due to its



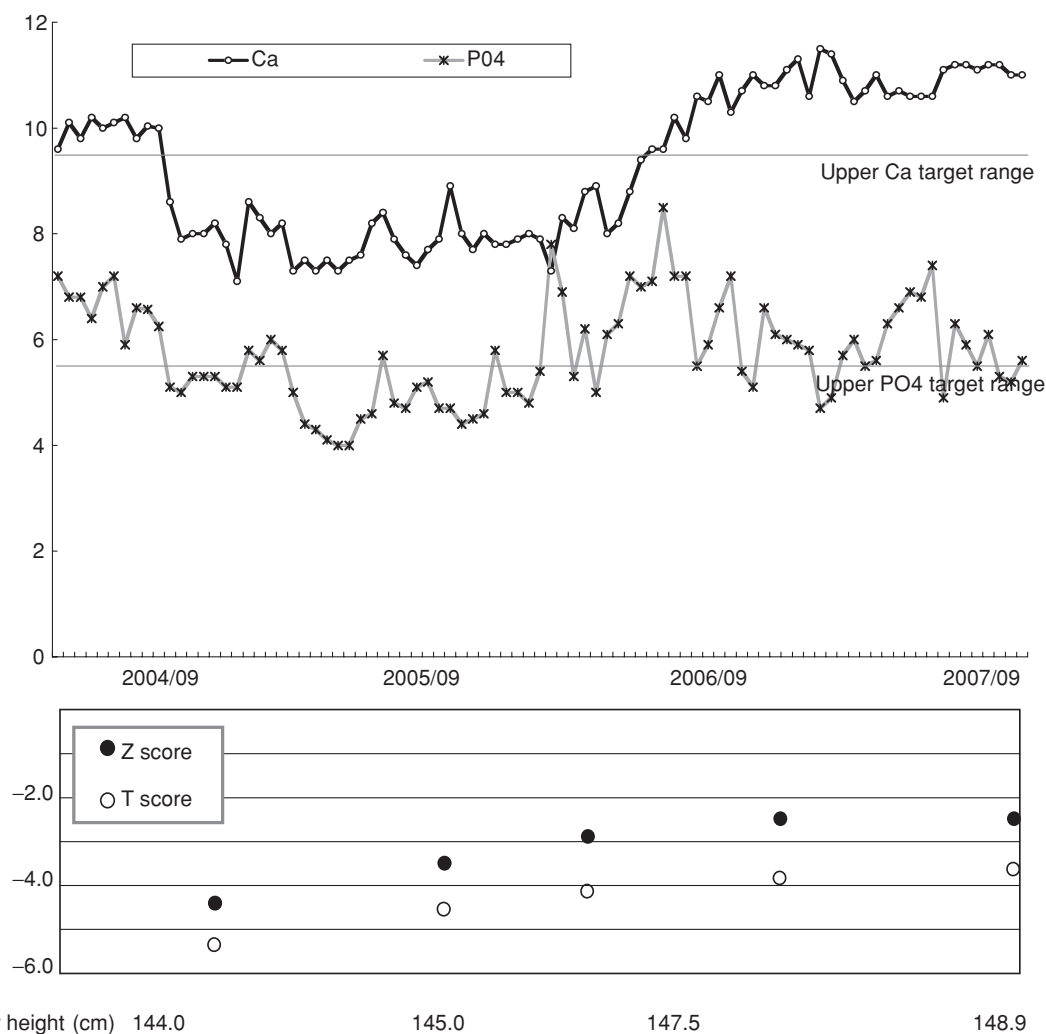
**Fig. 1.** Chest CT scan revealed multiple lung nodules indicative of multiple lung adenomas.

probable fertility; we thus decided to administer cinacalcet as oral therapy prior to its market launch in Japan. However, 1 year was required for acquisition of this drug. For this reason, her height decreased another 10 cm during the 1-year-waiting period.

Cinacalcet was started at a daily dose of 30 mg in September 2004, and titrated up to a dose of 120 mg/day. The patient remained on this high dose for 58 weeks; subsequently, her iPTH levels decreased, and the dose could be reduced stepwise to maintenance levels of 60 mg/day. During treatment with cinacalcet, the patient also regularly received other medications, including a phosphate binder (sevelamer, 5250–6750 mg/day), precipitated calcium carbonate (500–1500 mg/day) and maxacalcitol (22-oxacalcitriol 60 µg/week). Unfortunately, this calcium carbonate dose could not be increased due to the patient’s refusal.



**Fig. 2.** Changes in Ca, P, ALP, BAP and iPTH, before versus after treatment with cinacalcet. Measured serum Ca levels were adjusted by albumin levels as follows: when they were <4.0 g/dL: Ca = measured calcium levels + (4.0 – albumin levels) mg/dL.



**Fig. 3.** Changes in Ca, P, and BMD, before versus after treatment with cinacalcet.

Throughout the 1.6 years of treatment, serum levels of iPTH, alkaline phosphatase (ALP) and bone alkaline phosphatase (BAP) were persistently decreased (Figure 2), while Ca and P steadily increased (Figure 3). Thereafter, with the rise of Ca (>8 mg/dL), iPTH (which stayed in the 750–1500 pg/mL range) ultimately fell to 150–200 pg/mL. Similarly, ALP and BAP were normalized. As a consequence, bone pain gradually disappeared. Bone mineral density (BMD) was improved by administration of cinacalcet. Before this treatment, the BMD of the distal one-third of the radial bone on dual-energy x-ray absorptiometry (DEXA) was 0.349 g/cm<sup>2</sup> (T score, –5.7 SD), but after 3 years of cinacalcet administration, had improved to 0.432 g/cm<sup>2</sup> (T score, –3.7 SD).

## Discussion

We have demonstrated cinacalcet therapy to be effective for refractory sHPT due to multiple lung parathyroid adenomas. Our case showed severe hypocalcaemia and

hypophosphataemia with increases in ALP and BAP after initiation of cinacalcet, similar to the so-called hungry bone syndrome occasionally seen in classic SHPT following PTx [3]. In the hungry bone syndrome, the equilibrium between calcium efflux from and influx into the bone matrix is severely disrupted accompanied by rapidly falling PTH. Increased osteoclastic activity associated with osteitis fibrosa, elevated ALP and large parathyroid gland volume at the time of resection are predictors of developing this syndrome [3,4]. Consequently, it has been suggested that calcimimetics may induce this phenomenon [5,6].

Cinacalcet is an allosteric modulator of the CaSR. Cinacalcet increases CaSR sensitivity, lowers the threshold for activation by calcium and decreases PTH secretion [7]. A rat model and a clinical study demonstrated that the inverse sigmoid curve between plasma calcium ion (Ca<sup>2+</sup>) and serum PTH levels was simply shifted leftward by calcimimetic infusion [7,8]. This result suggested that lowering plasma Ca<sup>2+</sup> might induce a conformational change of the CaR, resulting in dissociation from G proteins

or loss of the binding site for cinacalcet. Our present case had prolonged hypocalcaemia. During severe hypocalcaemia, iPTH levels remained in the range between 750 and 1500 pg/mL. Thereafter, coinciding with the rise of Ca (>8 mg/dL), iPTH levels ultimately fell to 150–200 pg/mL. Her clinical course appeared to be consistent with this hypothesis.

In conclusion, cinacalcet was effective in this patient with refractory and inoperable sHPT. In addition, it improves their BMD and relieves bone pain.

*Conflict of interest statement.* None declared.

## References

1. Tominaga Y. Management of renal hyperparathyroidism. *Biomed Pharmacother* 2000; 54(Suppl 1): 25–31
2. Tseng CC, Huang JJ, Wang MC *et al.* Parathyroid carcinoma with multiple lung metastases. *Nephrol Dial Transplant* 1999; 14: 449–451
3. Cruz DN, Perazella MA. Biochemical aberrations in a dialysis patient following parathyroidectomy. *Am J Kidney Dis* 1997; 29: 759–762
4. Lazar ES, Stankus N. Cinacalcet-induced hungry bone syndrome. *Semin Dial* 2007; 20: 83–85
5. Goodman WG, Hladik GA, Turner SA *et al.* The calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. *J Am Soc Nephrol* 2002; 13: 1017–1024
6. Torres PU. Clinical experience with cinacalcet HCl. *Nephrol Dial Transplant* 2004; 19: v27–v33
7. Nagano N. Pharmacological and clinical properties of calcimimetics: calcium receptor activators that afford an innovative approach to controlling hyperparathyroidism. *Pharmacol Ther* 2006; 109: 339–365
8. de Francisco AL, Izquierdo M, Cunningham J *et al.* Calcium-mediated parathyroid hormone release changes in patients treated with the calcimimetic agent cinacalcet. *Nephrol Dial Transplant* 2008; 23: 2895–2901

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