

RECURRENT HYPERPARATHYROIDISM: CASE REPORT

Branko Bečejac, Mira Misjak, Velimir Altabas, Maja Berković, Gorana Mirošević and Milan Vrkljan

Department of Endocrinology, Diabetes and Metabolic Diseases, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – A 57-year-old man with a history of primary hyperparathyroidism, consequential chronic renal failure and associated chronic Hashimoto's thyroiditis presented with recurrent hypercalcemia. Hypercalcemia persisted despite three resections of enlarged parathyroid glands and multiple sclerosations of the remaining parathyroid tissue. The possible causes of persisting hypercalcemia include unrecognized asymmetric parathyroid hyperplasia, multiple parathyroid adenomas, however, parathyromatosis as a complication of parathyroid resection could not be ruled out. Dispersion of parathyroid tissue and growth of multiple parathyroid nodules could lead to primary hyperparathyroidism. With intermittent parenteral pamidronate normocalcemia was temporarily achieved, although fourth resection of parathyroid tissue and subtotal thyroidectomy eventually led to normocalcemia and normal parathyroid hormone levels in this patient.

Key words: Hyperparathyroidism – complications; Hyperparathyroidism – pathology; Hyperparathyroidism – surgery; Hyperplasia; Recurrence; Adenoma – complications; Calcium – blood; Case Report

Introduction

Surgical treatment of primary hyperparathyroidism (PHPT) is successful in up to 95% of cases¹. Failure of surgery may lead to either persistent or recurrent hyperparathyroidism. Persistent hyperparathyroidism is a consequence of (often unrecognized) asymmetric parathyroid hyperplasia, ectopic parathyroid tissue (localized within the thyroid gland or retroesophageally in the mediastinum), or additive parathyroid glands.

Recurrent primary hyperparathyroidism (12%-16%) occurs after a period of 6 to 12 months of postoperative normocalcemia due to insufficient resection of hyperplastic parathyroid glands, other parathyroid adenomas, and rarely parathyroid carcinomas or multicentric milary parathyromatosis caused by accidental rupture of encapsulated adenomas during previous surgery and tissue dispersion in the neck region²⁻⁴.

Neck fibrosis following initial surgery can lead to problems in imaging diagnostic procedures, thus requiring radical neck reoperations that are accompanied by

an increased risk of the recurrent nerve lesions and need of total thyroidectomy.

When reoperation of recurrent or persistent hyperparathyroidism is not possible or is considered to be too hazardous, medical management should be introduced. Calcitonin is effective, yet inactivating antibodies limit its long-term use. A better choice seems to be parenterally administered pamidronate, which can be used whenever hypercalcemia aggravates. In the most recent period, calcimimetics offer new options in treating hypercalcemia.

Case Report

B. Z., a 57-year-old man, was diagnosed with right-sided nephrolithiasis, renal failure grade I/II, and hypercalcemia up to 3.1 mmol/L (normal values below 2.6 mmol/L) during 1991. The parathyroid hormone (PTH) levels were elevated (554 pg/mL; normal values 20-90 pg/mL), and the diagnosis of enlarged left inferior parathyroid gland was established using sestamibi scanning. In 1991, the enlarged gland was surgically removed and on histopathology confirmed as parathyroid adenoma.

Until 1999, serum calcium levels were normal, afterwards hypercalcemia with total serum calcium levels of up to 3.18 mmol/L and ionized serum calcium levels

Correspondence to: *Branko Bečejac, MD*, Department of Endocrinology, Diabetes and Metabolic Diseases, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: ??

Received April 4, 2006, accepted May 26, 2006

of up to 1.64 mmol/L due to elevated PTH levels (315 pg/mL) were found again. Hyperfunction of the remaining parathyroid glands was considered and total parathyroidectomy was suggested. In 2000, an attempt at total parathyroidectomy failed, i.e. two enlarged glands were removed (the remaining left-sided gland, and the upper right-sided gland), but the fourth gland could not be visualized at the time. After some time, an enlarged parathyroid gland was found behind the inferior pole of the left thyroid lobe by using both ultrasound and sestamibi scanning. Sclerosations with 95% alcohol were performed on 12 occasions, without success. Hypercalcemia persisted (total serum calcium 3.73 mmol/L and ionized serum calcium 1.73 mmol/L after sclerosations). During March 2003, neck ultrasonography revealed hypochoic nodules in the postoperative scar, cytologically positive for parathyroid tissue. At that time, the patient was reoperated on and the left inferior parathyroid gland was removed, but hypercalcemia still persisted. The highest calcium level of 3.7 mmol/L due to PTH level of 741 pg/mL, with deterioration of the patient's general condition and renal function (serum creatinine up to 390 μ mol/L) was recorded in September 2003. Then the patient was rehospitalized and treated with alendronate and calcitonin. On control neck ultrasound performed in October 2003 two hypochoic nodules were found: one behind the middle third of the right thyroid lobe, and another one in the postoperative scar subcutaneously on the right side of the neck. Cytology of both nodules suggested parathyroid tissue. Surgical treatment was considered, however, continued conservative treatment was favored due to the high risk of complications such as recurrent nerve lesion and need of thyroidectomy. Subsequently, the patient received pamidronate parenterally, up to 60 mg daily, on a monthly basis, with an initially satisfying effect on calcium concentration. With this therapy, calcium level dropped gradually to 2.40 mmol/L.

During 2004 and 2005, the patient was treated conservatively with cyclic bisphosphonates intravenously (pamidronate) with a good initial effect on calcium levels, however, bone markers and PTH level remained elevated (917 pg/mL). Bone markers were elevated whenever investigated: in 2000, urinary deoxypyridinoline was 14.15 nmol/mmol creatinine (normal range 2.3-5.4 nmol/mmol creatinine); in 2003, it was markedly higher, reaching a level of 36.20 nmol/mmol creatinine; osteocalcin was also elevated in 2003, measuring 312

ng/mL (normal range 12-41 ng/mL); hydroxyproline in daily urine was also elevated, 367.30 mmol/24 h/m² (normal range 46-168 mmol/24 h/m²), suggesting the presence of metabolic bone disease.

DXA was performed in 1999, showing values within the normal range at the sites of femoral neck (T score +0.65) and lumbar spine (T score +0.59), but osteopenia was detected at distal radius (T score -2.15). In 2003, repeat DXA showed a decrease in T scores at the sites of femoral neck (T score -0.6) and lumbar spine (T score -1.0). After several months, hypercalcemia with ionized serum calcium up to 2.34 mmol/L and total serum calcium up to 4.71 mmol/L occurred again despite bisphosphonate therapy. PTH levels were extremely high (1007 pg/mL). Multi-slice computed tomography of the neck region showed several polycystic structures next to the left lobe of the thyroid. These structures were positive on sestamibi scans.

In 2005, the patient was reoperated on; extensive neck exploration and subtotal thyroidectomy were performed, with consecutive hoarseness due to the recurrent nerve lesion. Definitive histopathology findings indicated parathyroid hyperplasia and thyroid tissue. It was followed by rapid improvement of serum calcium levels (2.0 mmol/L) and serum PTH concentrations (67 pg/mL). There was no postoperative hypocalcemia. Thyroid hormone replacement was required (100 mcg LT4 daily) to maintain euthyroidism.

After one year, calcium levels (total serum calcium 2.4 mmol/L) and phosphates (0.8 mmol/L) remained normal, indicating normal PTH secretion. Even creatinine values decreased markedly (160 μ mol/L).

Although normocalcemia was eventually achieved in our patient, it still demands continuous follow up. PTH secretion seems to be normalized, indicating a remaining parathyroid tissue that may undergo hyperplasia and hyperfunction in the future.

Discussion

In this patient, the main problem was recurrent primary hyperparathyroidism. Elevated levels of total and ionized serum calcium as well as PTH persisted in spite of 3 parathyroid gland resections and 12 sclerosations of the remaining parathyroids with 96% ethanol. Ultrasonography, cytology, scintigraphy and computed tomography suggested several structures in the anterior neck positive for parathyroid tissue. Skeletal scintigraphy indicated diffuse metabolic hyperactivity, confirmed by high bone turnover markers, osteocalcin in particular.

Regarding patient history, several hypotheses about the causes of parathyroid enlargement and hyperfunction could be considered. Multiple adenomas⁵ of metachronous development could have been the possible cause of the disease. Normalization of hypercalcemia over eight years after the first parathyroidectomy and histopathology of the first removed parathyroid gland indicating adenoma could have been related to the disorder.

Otherwise, histopathology of the next removed parathyroid gland showed parathyroid hyperplasia. It is possible that asymmetric hyperplasia of all parathyroid glands was not initially recognized^{6,7}. Furthermore, parathyromatosis as a consequence of perioperatively ruptured capsule of the adenoma could not be excluded^{8,9}. Even ruptured parathyroid cysts can cause such a complication¹⁰. Low differentiated parathyroid carcinoma was ruled out in our patient¹¹.

The treatment of choice is surgery¹ (adenomectomy or subtotal parathyroidectomy). In cases when surgery is not possible or does not seem successful, conservative treatment is indicated. Avoiding thiazide diuretics and prolonged immobilization, adequate hydration, dietary calcium restriction below 1000 mg daily, phosphates, bisphosphonates and calcitonin are therapeutic options. Calcimimetics (e.g., cinalcet) are drugs of a new class offering hypocalcemic effects, but have not yet been introduced in clinical use. These drugs increase parathyroid cell sensitivity to extracellular calcium levels and inhibit PTH secretion¹.

References

1. AACE/AAES Task Force on Primary Hyperparathyroidism: the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons Position Statement on the Diagnosis and Management of Primary Hyperparathyroidism. *Endocr Pract* 2005;11:49-54.
2. DEDEURWAERDERE F, Van DAMME B. Histopathology of the parathyroid glands. *Acta Otorhinolaryngol Belg* 2001;55:95-101.
3. BORNSTEIN-QUEVEDO L, GAMBOA-DOMÍNGUEZ A, ANGELES-ANGELES A, REYES-GUTIÉRREZ E, VARGAS-VORÁCKOVA F, GAMINO R, HERRERA MF. Histologic diagnosis of primary hyperparathyroidism: a concordance analysis between three pathologists. *Endocr Pathol* 2001;12:49-54.
4. BARCLAY L. Unilateral approach favored for parathyroid surgery. *Ann Surg* 2002;236:543-51.
5. ASO Y, USHIYAMA T, NAKANO N, OHTA N, TAJIMA A. Preoperative diagnosis of localization of abnormal parathyroid glands. *Aktuel Urol* 1990;21 (Suppl):83-8.
6. BERGENZFELZ A, FORSBERG L, HEDERSTROM E, AHREN B. Preoperative localisation of enlarged parathyroid glands with ultrasonically guided fine needle aspiration for parathyroid hormone assay. *Acta Radiol* 1991;32:403-5.
7. TEZELMAN S, SHEN W, SHAVER JK, SIPERSTEIN AE, DUH Q-Y, KLEIN H, CLARK OH. Double parathyroid adenomas. Clinical and biochemical characteristics before and after parathyroidectomy. *Ann Surg* 1993;218:913-22.
8. WOOLNER LB, KEATING FR Jr, BLACK BM. Tumors and hyperplasia of parathyroid glands. *Cancer* 1952;5:1069-88.
9. REDDICK RL, COSTA JC, MARX SJ. Parathyroid hyperplasia and parathyreomatosis. *Lancet* 1977;1:5.
10. CLARK OH. Parathyroid cysts. *Am J Surg* 1978;135:395-402.
11. KEBEBEW E. Parathyroid carcinoma. *Curr Treat Options Oncol* 2001;2:347-54.

Sažetak

RECIDIVIRAJUĆI HIPERPARATIROIDIZAM: PRIKAZ SLUČAJA

B. Bečejac, M. Misjak, V. Altabas, M. Berković, G. Mirošević i M. Vrkljan

Prikazuje se 57-godišnji bolesnik s recidivirajućim primarnim hiperparatiroidizmom i posljedičnom kroničnom bubrežnom insuficijencijom. U tri navrata učinjena je ekstirpacija povećanih paratiroidnih žlijezda i višekratna sklerozacija preostalog paratiroidnog tkiva, uz i dalje prisutnu hiperkalcemiju. Moguća objašnjenja su da se kod bolesnika radilo o višestrukim adenomima paratiroidnih žlijezda koji su se razvili metakrono ili se od samog početka radilo o neprepoznatoj asimetričnoj hiperplaziji svih paratiroidnih žlijezda. Ne može se, međutim, isključiti niti paratiromatoza kao posljedica poslijeoperacijske rupturiranja kapsule adenoma, što je dovelo do rasapa i ponovnog rasta višestrukih paratiroidnih čvorova i recidiva primarnog hiperparatiroidizma. Bolesnik je uz intermitentnu parenteralnu terapiju pamidronatom bio u prolaznoj normokalcemiji, a nakon ponovne pojave hiperparatiroidizma učinjena je radikalna disekcija paratiroidnog tkiva i subtotalna resekcija štitne žlijezde, čime je uspostavljena normokalcemija i postignuta uredna razina paratiroidnog hormona.

Ključne riječi: Hiperparatiroidizam – komplikacije; Hiperparatiroidizam – patologija; Hiperparatiroidizam – kirurgija; Hiperplazija; Ponovno izbijanje bolesti; Adenom – komplikacije; Kalcijum – krv; Prikaz slučaja