

CASE REPORTS

Resolution of primary hyperparathyroidism following surgical removal of cervical thymus

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ABSTRACT

Recent research has emphasized the capacity of thymus cells of producing parathyroid hormone (PTH) if adequately stimulated, and have investigated the role of the so-called “thymic PTH”, produced by the medullary thymic epithelial cells (m-TECs). To the best of our knowledge, only a single case of well-documented PTH secretion from a thymoma causing primary hyperparathyroidism (PHPT) has been reported in the literature so far. We report here the case of a female patient with PHPT who underwent neck exploration for a suspected parathyroid adenoma. After surgery, a normalization of serum PTH concentration was observed, but the histological examination of the surgically excised mass revealed exclusively normal thymus tissue. The present case provides additional evidence of PHPT caused by an ectopic thymus.

Key Words: Thymic parathyroid hormone, Primary hyperparathyroidism, Thymus, Parathyroid, Hypercalcemia

1. INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders worldwide. It is biochemically characterized by elevated serum calcium levels and elevated serum parathyroid hormone (PTH) concentrations,^[1] whereas PTH serum levels are suppressed in all cases of non-parathyroid hypercalcemia.^[2] PHPT is classically associated with nephrolithiasis and nephrocalcinosis in over two-thirds of patients, and with *osteitis fibrosa cystica* in one-third of cases.^[3] Moreover, psychiatric, neurological, cardiovascular and gastrointestinal signs and symptoms can be also present.^[4] The most common causes of PHPT include single parathyroid adenoma that accounts for the 85% of the cases, multiglandular hyperplasia in 10%-15% of cases, and lastly carcinoma in 1% or less of the cases. In addition uncommon

familiar causes do exist, such as MEN-1 and MEN-2A.^[5]

We report here the case of PHPT apparently due to ectopic secretion of PTH by cervical thymus in a 32-year-old female affected by PHPT. 99mTc/99mTc-MIBI scintiscan led us hypothesize that it was due to a single parathyroid adenoma. Following its surgical removal, both hypercalcemia and hyper-PTH-emia restored; surprisingly histological examination of the surgically resected specimen revealed exclusively normal thymus. The diagnosis of neuroendocrine tumor was excluded.

2. CASE PRESENTATION

CA is a 32-year old female who initially presented to the Endocrinology Clinic, of the teaching hospital “G. Rodolico”, University of Catania, on September 2014 with a history

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of PTH. The clinical history of the patient had started 8 months before when she consulted a Nephrology Clinic for recurrent attacks of acute nephrolithiasis. Blood testing revealed PTH levels of 113 pg/ml (normal range: 15-65) and calcium of 10.4 mg/dl (normal range: 8.1-10.3). She underwent thyroid-parathyroid ultrasound scan that showed three different hypoechoic areas adjacent to the thyroid lobes. These nodules with regular margins had normal vascularization. One of them, next to the right lobe, measured 6 mm × 6 mm × 8 mm; the others, located next the left lobe, were of 8 mm × 11 mm × 17 mm and 5 mm × 7 mm × 8 mm. Thyroid gland volume was slightly higher than normal (17.6 ml) and 4 nodules were described in the left lobe. They measured 3 mm × 3 mm × 5 mm, 3 mm × 3 mm × 4 mm, 8 mm × 11 mm × 11 mm (with perinodular vascularization) and 4 mm × 4 mm × 5 mm respectively. A subsequent ^{99m}Tc/^{99m}Tc-MIBI scintiscan showed an increased uptake in the lower third of the left thyroid lobe. A bone mineral density test revealed a T-score of -0.1 in the lumbar spine and -0.3 in the left hip. Hence the patient was started on Cinacalcet 30 mg/daily and, a couple of weeks later, the dosage was increased to 60 mg/daily. However, she had a low compliance to the treatment because of nausea and vomiting. Consequently, on June 2014, the treatment was stopped and she was referred to the Surgery Unit of the University of Catania Teaching Hospital to be evaluated for parathyroidectomy. A neck magnetic resonance imaging showed a nodule of 13 mm in the lower third of the left thyroid lobe. At this point she complained acutely of back pain that was referred to nephrolithiasis.

At the end of September 2014, CA underwent surgery. The neck exploration was performed through a transverse cervical incision. Next to the left thyroid lobe, in correspondence to the site of the increased uptake observed with the ^{99m}Tc/^{99m}Tc-MIBI scintiscan, there was an oval-shaped, fully capsulated mass, macroscopically similar to a parathyroid adenoma. It was found to be in connection with the thymic corn through a cord. The nodule was excised, fixed in 10% buffered formalin and processed by conventional methods.

Haematoxylin and eosin (HE) stain revealed normal thymus with interspersed adipose tissue (see Figure 1). In addition, immunohistochemical analysis (avidin–biotin–peroxidase complex-ABC technique), using a monoclonal rat anti-human PTH antibody (clone 3B3; Dako Diagnostics BV, Glostrup, Denmark) as described elsewhere,^[6] was performed to evaluate the presence of PTH. Briefly, after microwave pretreatment and blockage of endogenous peroxidase activity, sections were incubated with the PTH antibody at room temperature. Next, they were incubated with rabbit

biotinylated anti-rat IgG and treated with the ABC standard kit (Vector, Amsterdam, The Netherlands). Peroxidase activity was visualized with 0.5% 3,3'-diaminobenzidine tetrahydrochloride (DAB; Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands) and H₂O₂ 0.3% in 0.05 M Tris-HCl. All sections were counterstained with Mayer's haematoxylin for 1 min. Notably immunohistochemical analyses did not reveal any PTH-positive cells. On the contrary, the cells of a histologically normal intra-thyroid parathyroid, obtained from a surgically excised thyroid of another patient with bilateral nodular goiter, were diffusely and strongly stained with PTH antibody, and thus served as external control.

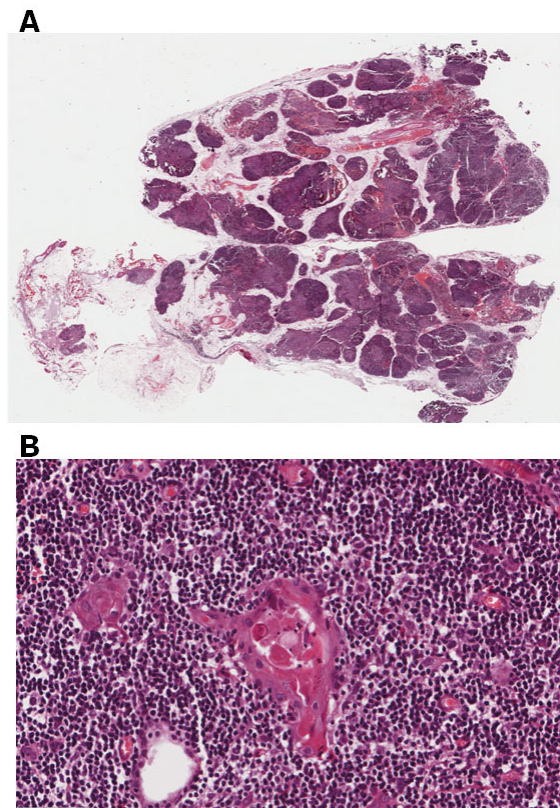


Figure 1. A. Low magnification of the mass surgically removed, showing normal thymus with interspersed adipose tissue (Haematoxylin and eosin staining, × 40 magnification); B. Higher magnification showing lymphocytes and Hassal's corpuscles (Haematoxylin and eosin staining, × 250 magnification)

The patient had an uneventful postoperative course. The follow-up showed a decreasing PTH serum levels at the 2nd postoperative month; then, after an increase at the 3rd month, a definitely reduction until a normalization of serum PTH levels starting from the 3.5th month was observed. In addition, the patient was eucalcemic and no alteration of phosphorous levels was detected during the post-operative follow-up. A

second $^{99m}\text{Tc}/^{99m}\text{Tc}$ -MIBI scintiscan performed on January 2015 did not show any increased radionuclide uptake. At the 21th post-operative month, an increase in PTH and calcium serum levels was registered (see Figure 2, panel A), resembling a relapse of hyperparathyroidism. However, the $^{99m}\text{Tc}/^{99m}\text{Tc}$ -MIBI scintiscan performed on August 2016 did not show any increased pathologic uptake, and the PTH and calcium serum levels gradually and spontaneously normalized. Such results led us to require chromogranin A and neuron specific enolase (NSE) to exclude the diagnosis of neuroendocrine tumor secreting PTH, but they were within the normal range. The follow-up lasted two years.

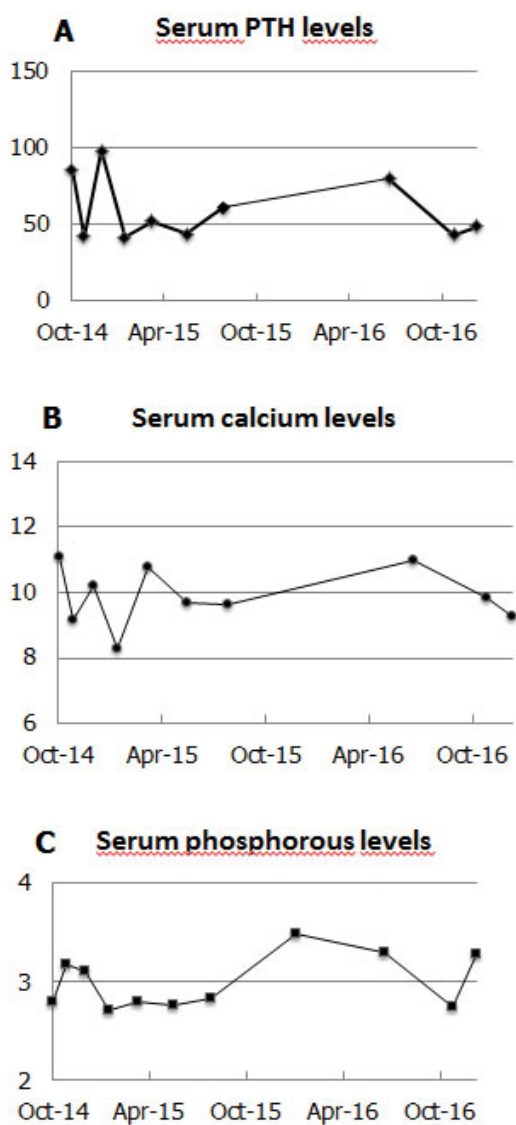


Figure 2. Serum parathyroid hormone (PTH, pg/ml) (A), calcium (mg/dl) (B) and phosphorous (mg/dl) (C) levels after surgery. PTH, calcium and phosphorous normal range are 15-65 pg/ml, 8.4-10.2 mg/dl, 2.7-4.5 mg/dl, respectively

3. DISCUSSION

Thymus and inferior parathyroid glands share the same embryologic origin (third pharyngeal pouch) and are intimately anatomically connected, whereas the superior parathyroid glands originate from the fourth pharyngeal pouch. Their common embryological origin could explain the reason why the most common ectopic site of parathyroid adenomas is the thymus.^[7] Moreover, a few cases of concurrent thymus and parathyroid pathology, such as thymoma and parathyroid adenoma with or without miastenia gravis, are described in the literature.^[8-10]

We report a case of apparent PTH secretion from thymus tissue. In fact, the normalization of PTH serum levels after surgery, the post-operative eucalcemic state and the absence of an increased uptake in the second and third post-operative $^{99m}\text{Tc}/^{99m}\text{Tc}$ -MIBI scintiscan led us to hypothesize that the mass surgically removed overproduced PTH and was the cause of the PHTP. Although it was macroscopically similar to a parathyroid adenoma, according to histological examination, the whole tissue removed was composed of normal thymic tissue with interspersed adipose tissue. Moreover, the presence of parathyroid cells in the excised tissue was excluded by immunohistochemistry.

A case of PTH secretion from a thymoma has been already documented by Rizzoli and colleagues. They reported a case of PHTP affecting a 25-year-old-male, caused by a superior retrosternal tumefaction surgically removed. Histological examination showed a predominantly epithelial thymoma without any detectable parathyroid glands. Tumor extracts contained immunoreactive PTH material, but PTH-positive cells were absent. Northern blot analysis revealed a PTH messenger ribonucleic acid transcript to a size similar to that found in adenoma or hyperplasia.^[11] Moreover, chromogranin A was absent. These results support the ectopic production of authentic PTH (1-34) by a thymoma, indicating a novel tumoral cause of PHTP.

Nevertheless, is thymic tissue capable of produce PTH? Moreover, what is its significance? Recently, the extra-parathyroid PTH production in the thymus (the so called "thymic PTH") has been described^[11] to explain the higher than expected survival rate for a parathyroid *Gcm2*^{-/-} mutants mice (*Gcm2* is required for the differentiation and survival of parathyroid precursor cells^[12]). According to these authors, thymic PTH could represent an auxiliary source of PTH and could extend the survival rate of these mice. They propose that its production may derive from two different mechanisms: (i) the incomplete separation of parathyroid and thymus organs during organogenesis resulting in isolated, misplaced parathyroid cells often attached to the thymus;

(ii) the expression of PTH from medullary thymic epithelial cells (mTECs). Human embryos analysis of thymus and parathyroid organogenesis indicate that these mechanisms may be also true for human parathyroid development model.^[12] mTECs express different ectodermal, endodermal and neuroectodermal derivatives that play an important role in maintaining self-tolerance.^[13,14] Therefore, it is believed that m-TECs PTH could act like a self-antigen in the negative selection process.^[12] Accordingly with Liu and colleagues, while parathyroid cells localized into the thymus produce PTH in a Gcm2-dependent manner, differentiated mTECs express PTH independently of Gcm2, in a FoxN1-dependent manner. Since thymus-derived PTH ameliorated the lethality phenotype of Gcm2^{-/-} mice, and since it totally derives from m-TECs,^[12] it can be concluded that the prolonged survival rate of mutant mice is entirely due to PTH produced by m-TECs, playing a possible role in serum calcium physiology.

In addition to m-TECs, it seems that also epithelial cells lining thymic cysts do express PTH, as well as calcitonin and thyroglobulin.^[15] Despite morphological and organizational differences, conventional m-TECs and thymic cysts epithelium display considerable phenotypic similarities and a history of FoxN1 expression. Seeing as parathyroid and follicular thyroid epithelial cells differentiation is based on FoxN1 expression too, it can be derived that FoxN1 expression per se is not a definitive marker for thymic lineage differentiation among pharyngeal endoderm derived epithelial tissues,^[15] but it represents a common marker for thymus, thyroid and parathyroid development. This thymus and parathyroid common developmental factor could prob-

ably explain thymic cells capacity of producing PTH under specific stimuli.

Indeed, a recent study showed that thymus cells could be considered as parathyroid-like precursor cells since, if adequately stimulated, they are capable of secreting PTH. The authors of this research treated human thymus cells utilizing 13 weeks exposure to activin A and soluble sonic hedgehog (Shh). The so obtained differentiated cells expressed PTH, calcium sensing receptor, chemokine receptor type-4 (CRCR4) and chorian-specific transcription factor (GCM2). Moreover, these cells responded as parathyroid cells to physiologic stimuli, suppressing the PTH secretion in response to increased calcium concentration.^[16] On this account, the authors underline the possibility of a therapeutic role of this new parathyroid cells obtained from the thymus tissue to restore parathyroid function in cases of hypoparathyroidism.

In conclusion, thymus tissue that was removed from our patient was included in a capsulated cervical mass, next to thyroid lobe, anatomically connected to thymus through a cord and macroscopically similar to a parathyroid adenoma. This tissue may represent a remnant of pharyngeal endoderm that has not been incorporated during thymic organogenesis and it could not have lost or could have acquired the capacity of producing PTH. At the lights of the evidence previously discussed, probably a novel tumoral cause of PHTP does exist and the role of "thymic PTH" should be examined in depth.

CONFLICTS OF INTEREST DISCLOSURE

The authors have no competing interests to declare.

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