

## Parathyroid cancer as rare cause of primary hyperparathyroidism. Case report and review of the literature

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**SUMMARY:** Parathyroid cancer as rare cause of primary hyperparathyroidism. Case report and review of the literature.

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*Primary hyperparathyroidism (PHPT) due to parathyroid carcinoma is rare, and affects more frequently women in their 4th-5th decades of life. Parathyroid cancer (PC) accounts for 0.5% up to 5% of the patients with primary hyperparathyroidism (PHPT). Diagnosis of PC is not easy, and a lot of patients with PHPT receive no pre-operative or intra-operative diagnosis of malignancy. Most of PC are hyperfunctioning, with marked serum PTH levels, and symptoms occurs more frequently than in benign disease. We report the case of a 52 years old woman that underwent a single parathyroidectomy for hyperfunctioning gland. Histological examination revealed carcinoma.*

*Parathyroid carcinoma is rare and surgery represent the only curative approach, although there can be a local recurrence of the disease. A pre-operative diagnosis is not easy, and many features that suggest the diagnosis of malignancy are controversial. According to the literature, we think that the cure of the parathyroid cancer is difficult to achieve.*

*After two years of follow-up, our patient is in good conditions and has no evidence of disease. A careful follow up is of primary importance to diagnose the local recurrence of disease and perform a second surgical treatment, to achieve the control of hypercalcemia, which causes severe metabolic alterations and visceral lesions until the death.*

**RIASSUNTO:** Carcinoma paratiroideo: una causa rara di iperparatiroidismo primario. Caso clinico e revisione della letteratura.

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*L'iperparatiroidismo primario raramente è causato da un carcinoma della paratiroide, che colpisce più frequentemente le donne nella 4<sup>a</sup>-5<sup>a</sup> decade di vita. Il carcinoma delle paratiroidi si riscontra infatti nello 0.5% fino al 5% dei pazienti con iperparatiroidismo primario. La diagnosi di carcinoma non è semplice, e in molti pazienti con iperparatiroidismo primario non è possibile né pre-, né intra-operatoriamente. Molti carcinomi paratiroidi sono iperfunzionanti, con elevati livelli ematici di paratormone, e quindi sintomatici più frequentemente rispetto alle forme benigne. Riportiamo il caso di una donna di 52 anni sottoposta a paratiroidectomia della unica ghiandola iperfunzionante, in cui l'esame istologico ha rivelato un carcinoma.*

*In questi casi la chirurgia rappresenta l'unica terapia efficace, anche se è frequente una ripresa locale di malattia. La diagnosi pre-operatoria non è semplice e molti elementi che ne suggeriscono la malignità sono controversi. In accordo con quanto riportato in letteratura, riteniamo che la guarigione definitiva del carcinoma delle paratiroidi sia difficilmente conseguibile.*

*Dopo due anni di follow-up la nostra paziente è in buone condizioni generali e libera da malattia. Un accurato follow-up è di fondamentale importanza per una diagnosi tempestiva di ripresa di malattia e per attuare un reintervento con il fine di ottenere il controllo dell'ipercalcemia che può essere causa di complicanze anche letali.*

**KEY WORDS:** Parathyroid cancer - Hyperparathyroidism - Surgery - Follow-up.  
Carcinoma delle paratiroidi - Iperparatiroidismo - Chirurgia - Follow-up.

### Introduction

A single glandular adenoma or hyperplasia are the most frequent cause of primary hyperparathyroidism

(PHPT). It is rarely caused by hyperfunctioning carcinoma, that accounts for 0.5% up to 5% of the patients with PHPT. A pre-operative diagnosis is difficult, and many features of malignancy are discussed. The first case was described over 60 years ago, but because of its rarity is difficult to establish clinical, histopathological and radiologic criteria of malignancy. Most of PC are hyperfunctioning, with marked serum PTH levels; a palpable mass also suggest malignancy. Surgical approach of PC is the gold standard treatment, with *en*

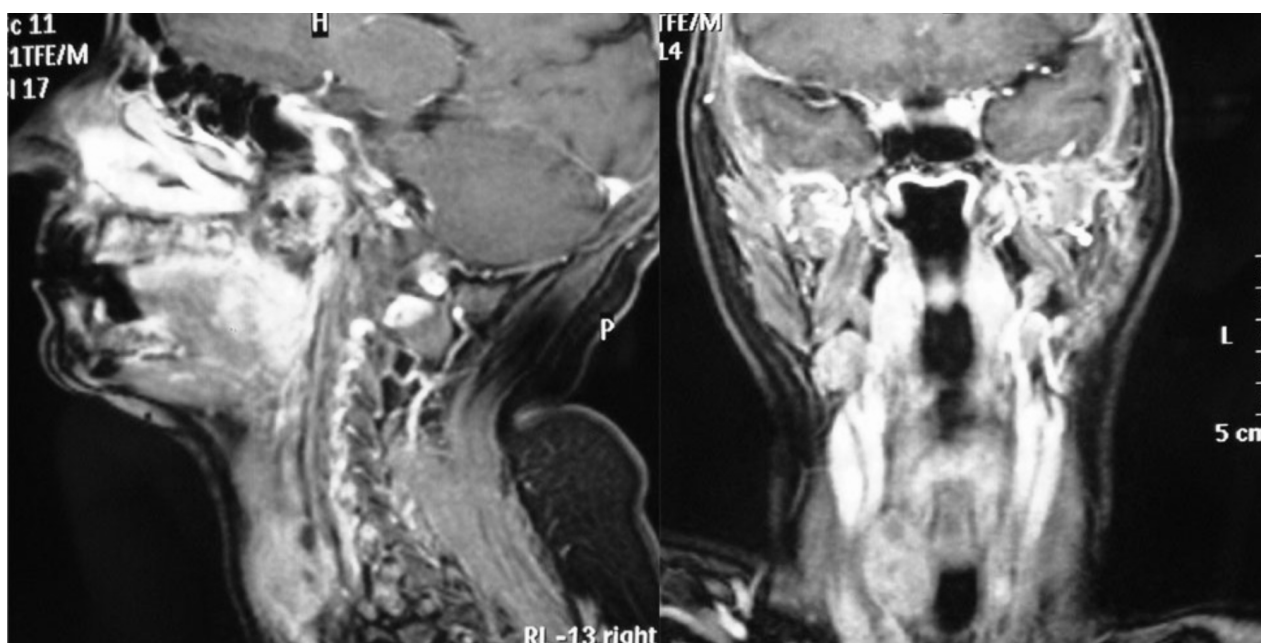


Fig. 1 - MRI scan: a nodular image of diameter 4 cm, with clear borders and dishomogeneous signal intensity and enhancement, next to the right lobe of the thyroid gland.

*bloc* resection of pathologic parathyroid gland, ipsilateral thyroid lobe and muscles.

Local recurrence occurs in up to 30%, in the primary site rather than in distant ones, and can be treated with a palliative surgical reexploration.

Chemotherapy and radiotherapy are not able to control local recurrence or distant metastases.

## Case report

### *Clinical features and diagnostic work-up*

A 52 years-old female was referred to us in October 2006 with a diagnosis of primary hyperparathyroidism (PHPT) and a single parathyroid gland mass, suspicious for adenoma. The patient complained of profound asthenia at the legs over the past 2 years. About 3 months before, she had suffered of dysphonia and sense of obstruction in the throat, bone pain and demineralization.

Ultrasonography of the neck showed an asymmetry of the thyroid gland with marked prevalence of the right lobe, and dishomogeneous structure. Close to the upper third of the right lobe there was an hypoechogenic nodule, with regular and clear borders, sized of 28x16 mm. Ecocolor-Doppler fluximetry showed widespread intensity of blood flux around and inside the nodule (Pattern III). Also there were other little thyroid nodules. A fine needle aspirate (FNAB) was made on this nodule, with result C3 (strips and microcytologically of microfollicular nodule with anisokaryosis and solid-trabecular architectural pattern). Immunohistochemistry reaction was focally positive for galectin 3. Laboratory tests showed marked hypercalcemia (13.5 mg%, range 8.6-10.3), hypophosphoremia (2.3 mg%, range 2.6-4.5), hypercalciuria (359 mg/24h, range 50-250), elevated serum Parathormone (PTH) (2039 pg/mL, range 9-70). MRI scan of the neck, showed a nodular image of diameter 4 cm, with clear borders and dishomogeneous signal intensity and enhancement, close to the right lobe of

the thyroid gland (Fig. 1). Clinical diagnosis was of primary hyperparathyroidism maybe caused by parathyroid hyperfunctioning adenoma.

At admission, laboratory tests were repeated, confirming hypercalcemia (13.9 mg/dL, range 8.05-10.1), hypophosphoremia (1.9 mg/dl, range 2.5-4.9), elevated blood levels of PTH (798 pg/mL, range 6.4-52) and serum alkaline phosphatase levels (803u/L, range 50-136). Blood levels of thyroid hormones were normal. At physical examination a palpable mass in the right side of the neck was evident, and dysphonia was also perceptible.

A laryngoscopic exam revealed lower motility of the right vocal cord. Endocrinologic evaluation confirmed the diagnosis of PHPT. To make clear on the thyroid and parathyroid disease, a scintigraphy with  $^{99m}\text{Tc}$ -Sestamibi (740 MBq) and  $^{99m}\text{TcO}_4$  (110 MBq) was made. The result was that thyroid gland was normal for site, size and symmetry of the lobes. Scintigraphy with  $^{99m}\text{Tc}$ -Sestamibi showed a fixation area in the upper third of the right lobe after 20 min.; after 2 hours this fixation area persisted in the same site. The digital removal image confirmed the presence of selective fixation of the lipophilic cation in the upper third of the right thyroid lobe (Fig. 2). The scintigraphic diagnosis was of hyperfunctioning right upper parathyroid gland. The right upper parathyroid excision was the treatment of choice. Clinical and pre-operative conditions of the patient were good, and anesthesiological risk was ASA II.

### *Surgical treatment*

With the patient in supine position and extended neck, a Kocher incision was made. At a first examination, behind the thyroid right lobe there was a parathyroid mass. After a careful dissection, an avascular split layer was found between thyroid and upper parathyroid, that was easily isolated. This gland was brownish and increased in consistence. The lower right parathyroid, appeared normal. The right thyroid lobe was thin, compressed by the enlarged parathyroid. After laryngeal recurrent nerve identification, the right upper parathyroidectomy was performed.

Post-operative outcome was regular. In the 1<sup>st</sup> post-operative day,

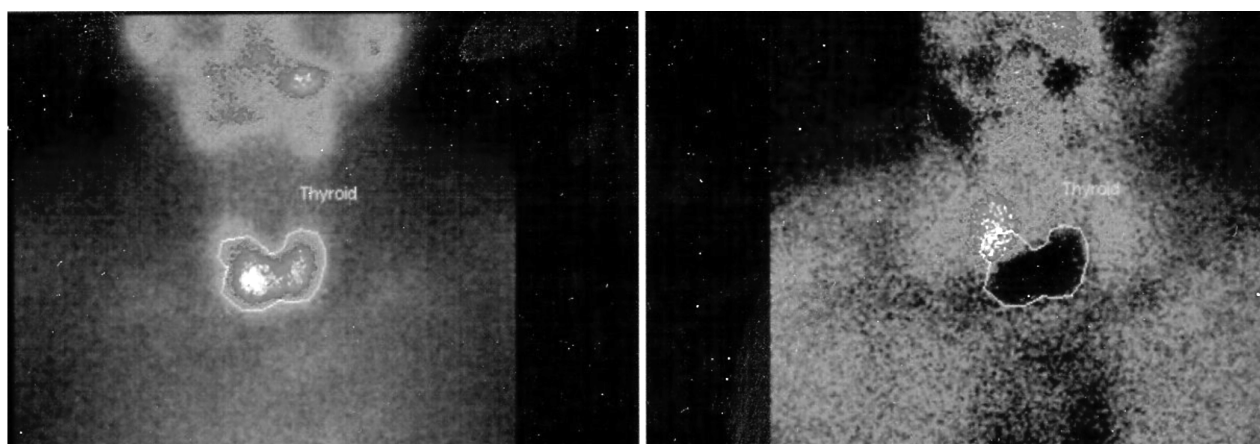


Fig. 2 - A fixation area of the lipophilic cation in the upper third of the right thyroid lobe.

blood level of parathormone resulted in 6.4 pg/mL (range 6.4-52); calcemia was 9.5mg/dL (range 8-10.5). Although normal values of calcemia, the patient had hypocalcemic crisis with swarming and tetanic contraction of the hands, quickly resolved with e.v. calcium gluconate; then, we decided to give oral calcium (1 g/tid) and calcitriol (0.25mcg/bid) even with normal calcemia, until the symptoms were resolved. These symptoms became slighter and slighter, until disappearing after 10 days.

An endocrinologic evaluation was repeated, and these unexpected symptoms were attributed to the "hungry bone syndrome". The only therapy was oral administration of calcium until symptom's complete resolution. The day after parathyroidectomy, the voice improved.

The patient was discharged in good conditions, and got oral administration of calcium and calcitriol, step by step reduced, based on level of calcemia.

#### Pathology

At histological grossly examination, the nodule appeared yellow-brownish, weight 5,00 grams, diameters 28x20x15 mm. At section, there were two white-greyish areas, with vanished borders, diameters 15 and 13 mm..

The diagnosis after microscopic examination was of chief cells parathyroid carcinoma, with endovascular permeation; resection margins were clear from disease. Immuno-histochemistry tests revealed positiveness of the neoplastic cells for parathormone.

#### Follow-up

After 3 months, the patient underwent an ultrasonography of the neck, which revealed hyperecogenous signal behind the right thyroid lobe, referable to cicatricial results, and no pathologic laterocervical lymphnodes. PTH blood level was high, 101 pg/mL (range 6.4-52). Then, the patient underwent a scintigraphy with <sup>99m</sup>Tc-Sestamibi (370 MBq) and <sup>99m</sup>TcO<sub>4</sub> (148 MBq), which revealed an hypofunctional right thyroid lobe referable to cicatricial results, and the absence of hyperfunctioning parathyroid tissue. Voice quickly improved by logopedic exercises. After 6 months PTH levels were normal, as ultrasonography too.

A careful follow-up was performed every three months. After 2 years, the patient is in good conditions and laboratory tests continue to reveal normal values of serum PTH. Ultrasonographic examination of the neck is normal too, without recurrence of disease and pathologic laterocervical lymph nodes. The patient get oral administration of levotiroxin 50 mcg/die because of hypofunctioning thyroid nodules.

## Discussion

Primary hyperparathyroidism (PHPT) is frequently caused by a single adenoma or hyperplasia, rarely by carcinoma, and affects more frequently women in their 4<sup>th</sup> - 5<sup>th</sup> decades of life (1). Parathyroid cancer (PC) is a rare endocrine malignancy, commonly hyperfunctioning, accounting for 0.5% up to 5% of the patients with primary hyperparathyroidism (PHPT) (2). Diagnosis of PC is not easy, infact 86% of the patients with PHPT receive no pre-operative or intra-operative diagnosis of malignancy (3, 4). There are no sexual differences in patients with PC, despite the female predominance of benign PHPT, but patients with PC are 10 years younger than those with benign PHPT. Most of PC are hyperfunctioning, with marked serum PTH levels, and symptoms occurs more frequently than in benign disease (5).

The first case was described by Armstrong over 60 years ago (6), but because of its rarity, although there are many studies which try to establish clinical, histopathological and radiologic criteria of malignancy, pre-operative diagnosis of PC is difficult. The results of these studies are doubtful and not always useful to allow an accurate pre-operative diagnosis of PC.

Surgical approach of PC is the current gold standard treatment, with *en bloc* resection of parathyroid gland, ipsilateral thyroid lobe and muscles. Histological features for malignancy were proposed by Schantz and Castleman (7) (Tab. 1): local invasion of contiguous structures, nodal or distant metastases, capsular or vascular invasion, fibrous trabeculae, high mitotic pattern.

Clinical findings for pre-operative suspicious of PC are: laryngeal recurrent nerve palsy, palpable mass, tumor size >3cm, calcium >14mg/dL, severe hyperparathyroidism, elevated levels of alkaline phosphatase (6). Intra-operative findings for malignancy are: local infiltration, greyish color, firm mass. Pre-operative imaging



TABLE 1 - HISTOLOGICAL FEATURES OF MALIGNANCY OF PARATHYROID MASS.

Local invasion of contiguous structures
Nodal or distant metastases
Capsular or vascular invasion
Fibrous trabeculae
High mitotic pattern

study with ultrasonography, Tc<sup>99m</sup>-sestamibi scintigraphy and CT scan can't make differential diagnosis between benign disease or malignancy. Tc<sup>99m</sup>-sestamibi scintigraphy is the most sensitive imaging modality used for localizing abnormal parathyroid tissue, with an accuracy of 90% (5). Sestamibi is a lipophilic cation that accumulates almost exclusively in the mitochondria; the oxyphil cells have an intensely eosinophilic cytoplasm rich of mitochondria. Principal cells are the active endocrine cells, with slight eosinophilic cytoplasm containing few mitochondria. A positive sestamibi scan is more frequent in adenomas rich in oxyphil cells than in predominance of chief cells (8). In absence of metastatic disease, it is difficult to establish a pre-operative diagnosis of PC. Agarwal et al. (9) examined prospectively 100 patients with PHPT, finding only 4 cases of PC. Clinical, biochemical, radiological and pathological features were examined, but there were no significantly differences among adenoma, hyperplasia and carcinoma. Only the tumor/PTG (parathyroid total gland) weight (mg) in patients with carcinoma (15,080 ± 5,638) was significantly higher when compared with adenoma (5,724 ± 1,257) and hyperplasia (3,310 ± 0,655) ( $P=0.002$ ).

Even if histological patterns were established by Schantz and Castleman (7), it is often difficult to make diagnosis of PC only on the basis of histology; infact, one of these findings can be seen in adenomas, but the presence of several findings in the same histological picture increase the possibility of malignancy (10). Lang and Lo (5) reviewed the literature on parathyroid cancer. The clinical presentation with symptoms of hypercalcemia, including anorexia, weight loss, fatigue, weakness, nausea, vomiting, bone pain, polyuria and polydipsia, complications such as pathologic fracture, renal colic, acute pancreatitis, peptic ulcer, occur more frequently than in benign disease. A palpable neck mass is present in up to 50% of PC; hoarseness of voice due to recurrent laryngeal nerve palsy increase the possibility of malignancy; cervical lymph node metastases are present in 15-20% of cases. Besides, pre-operative PTH level and gland weight seems to be predictive factors of malignancy. However, up to 30% of cancers haven't these characteristic features and benign disease can be similar to malignancy; then, a definitive diagnosis based on clinical or biochemical criteria is virtually impossible.

In view of the complexities about the diagnosis of PC, the most reliable way of diagnosing it is the demonstration of contiguous invasion or distant and lymphnodal metastases (9). In a retrospective analysis of 168 patients treated surgically for PHPT, Chang et al. (6) found 8 cases of PC. The mean age was 58.1 years (range 36-82 years), a mean calcium level of 11.57mg/dL and a mean PTH level of 623 pg/dL (88-2095 pg/dL). All 8 cases were hyperfunctioning PC but none had symptoms of hypercalcemia, and only in 25% (2 cases) a palpable mass was present. Although all eight patients underwent ultrasonography and sestamibi scan, none was suspicious for PC. At histological examination, all the PC presented at least two histological criteria for malignancy, and a mean size of 2.18 cm, lower than the one proposed for malignancy; all cases had signs of vascular or capsular invasion and mitotic pattern was high in 50%.

PC should be considered for differential diagnosis in asymptomatic PHPT, but the absence of severe hypercalcemia and symptoms should not rule out PC. Intraoperative frozen section with finding of high mitotic pattern will suggest the diagnosis, but surgical examination is very important for a radical or conservative treatment. Local recurrence occurs in up to 30%, in the primary site rather than in distant ones, but can be treated with a palliative surgical reexploration. However, Cohn et al. (11) demonstrated that not all patients need a prophylactic radical neck dissection, because there is no improvement in survival rate and morbidity. Hundahl et al. (4) demonstrated that in 286 cases of PC, only 15.2% of the patients that underwent lymph nodes dissection had metastases at the first excision, while 32% had metastases at reexploration; than, lymphnodal dissection is recommended only in cases of evident lymphnodal metastases. Pelizzo et al. (2) also confirmed a low rate of lymphnodal metastases at first surgery and reexploration.

A new challenge is the genetic screening; there isn't a specific gene involved in the cancerogenesis of PC, but in sporadic cases of PC there is mutation of *HRPT2* gene(12). About the follow-up, for hyperfunctioning PC biochemical markers (S-Ca, PTH) are more important than image techniques (ultrasonography, Scintigraphy, CT scan) (2, 5). Survival rate at 5 and 10 years is variable, 35-85.5% (2, 13). Chemotherapy and radiotherapy are not able to control local recurrence or distant metastases (2, 5).

## Conclusions

We reported this case of parathyroid cancer because it's a rare neoplasm and because as described by other authors we had some difficulties to make diagnosis of malignancy. According to the literature, we think that the cure of the parathyroid cancer is difficult to achieve.

ve. After two years of follow up the patient is in good conditions and has no evidence of disease. Besides, recurrence is the natural cancer history.

The aim of our careful follow up is to diagnose the

local recurrence of disease so that we can perform a second surgical treatment, to achieve, the control of the hypercalcemia, which causes following diseases and death.

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