Parathyroid Carcinoma: Case Report and Literature Review

Sofía Saccone1; Nicolas Tarigo2; Vanesa Soto1; Andres Salom1; Alvaro Ronco1; Nicolas Geribaldi1; Marcelo Pontillo2; Javier Rodríguez3; Gabriela Mintegui1*

1Department of Endocrinology and Metabolism, School of Medicine, University of the Republic (UdelaR) Montevideo, Uruguay.
2Department of Surgery, School of Medicine, University of the Republic (UdelaR), Montevideo, Uruguay.
3Unit of Oncology and Radiotherapy, Pereira Rossell Women’s Hospital, Montevideo, Uruguay. School of Medicine, CLAEH University, Prado and Salt Lake, Maldonado 20100, Uruguay.
4Department of Imaging, School of Medicine, University of the Republic (UdelaR), Montevideo, Uruguay.

*Corresponding Author: Gabriela Mintegui
Department of Endocrinology and Metabolism, School of Medicine, University of the Republic (UdelaR) Montevideo, Uruguay.
Tel: +23-48064871001; Email: chymaoby@yahoo.com

Abstract...

Parathyroid carcinoma is a malignant tumor derived from the parenchymal cells of the parathyroid glands. It represents one of the less frequent causes of primary hyperparathyroidism, with an incidence of 0.36 per 10 million people. Knowledge about the history of the disease and prognostic factors is currently limited. It should be suspected in a patient with marked hypercalcemia and very high parathyroid hormone (PTH), with a large tumor, and with bone and kidney repercussions that should be evaluated initially. The mainstay of treatment is surgery, both as initial treatment and for treatment of recurrence or metastasis; this should include parathyroidectomy or in bloc resection of the parathyroid mass, the surrounding capsule, and includes ipsilateral thyroid lobectomy, and any adjacent tissue that the tumor has invaded. Patients should be followed up on the possibility of recurrence by measuring serial calcium, serum PTH, and at least one thyroid ultrasound once a year. The disease can recur in a third of patients, presenting a cure with a second surgery. We herewith analyze a 55-year-old patient with a history of multiple cardiovascular diseases and chronic kidney disease, who presents with primary hyperparathyroidism with very high serum concentrations of calcium and PTH, in whom left lobectomy and parathyroidectomy with in bloc resection were performed due to suspicion of malignancy, whose pathological anatomy showed a parathyroid carcinoma.

Keywords: Hyperparathyroidism; Parathyroid carcinoma; Parathyroidectomy; Hypercalcemia.
Introduction

Parathyroid carcinoma is a malignant tumor derived from the parenchymal cells of the parathyroid glands and represents one of the less frequent causes of primary hyperparathyroidism. In recent years, the incidence of parathyroid carcinoma, according to the Surveillance, Epidemiology, and End Results (SEER) registry from 2000 to 2012, was 0.36 per 10 million people [1]. Because it is a rare disease, knowledge about this carcinoma’s history and prognostic factors is currently limited [2].

Next, a clinical case of parathyroid carcinoma in a 55-year-old man is presented, and an updated bibliography is reviewed.

Clinical case

This is a 55-year-old male patient with a medical history of high blood pressure, ischemic stroke, chronic obstructive artery disease in the lower limbs, heart failure with a left ventricular ejection fraction of 28%, and cardio defibrillation in 2014. Due to cardiorespiratory arrest in the context of ventricular fibrillation, the patient is currently receiving pharmacological treatment with acetylsalicylic acid, statins, cilostazol, captopril, and furosemide. He also has stage IV chronic kidney disease (CKD) of vascular etiology, primary hypothyroidism in treatment with levothyroxine, and a former heavy smoker diagnosed with a chronic obstructive pulmonary disease by spirometry but without treatment.

In assessing this patient’s CKD, the paraclinical blood studies show plasma parathyroid hormone (PTH) of 2285 pg/mL and calcemia of 13/14.2/14.4 mg/dL leading us to reach the diagnostic conclusion of hyperparathyroidism. Other blood tests to highlight are: albumin 3.8 g/dL, phosphorus 2.4 mg/dL and calciiuria 240 mg/24 h, vitamin D 9 ng/mL, creatinine 2.52 mg/dL and urea 79 mg/dL, sodium 139 mEq/L, potassium 4.8 mEq/L, chlorine 109 mEq/L, TSH 7.10 µUI/ml and FT4 1.11 ng/dl.

The thyroid ultrasound (Figure 1) of the patient shows a solid, oval nodular image, with lobulated contours, hyperechoic, 37 x 19 x 18 mm linked to the posteroinferior face of the lower third of the left lobe of the thyroid gland, in a projection of the left parathyroid lodge that could correspond to an adenoma. Still, other etiologies cannot be ruled out due to the nodule’s atypia characteristics.

The evaluation is completed with a parathyroid scintigram with single-photon emission computed tomography (SPECT-CT) that confirms hyper-uptake in the left parathyroid region (Figures 2,3).

Regarding repercussions at the bone and renal level due to his hyperparathyroidism, in radiographic studies, there is an alteration in the density of the bones of the cranial vault, subperiostal resorption in the left hand, at the level of the spine, osteosclerosis of the vertebral plates and lytic lesions corresponding to brown tumors (Figure 4). In a renal ultrasound, multiple microcalcifications are identified in the cortex and the medulla that could be related to nephrocalcinosis, without ruling out that some of the medullary calcifications are lithiasis.

Given the findings described, the treatment with left lobectomy and in bloc left parathyroidectomy was decided due to the possibility of parathyroid carcinoma. Surgery revealed a pathological left parathyroid gland, measuring 3 x 2 cm. From the biochemical measurements, preoperative PTH of 1818 pg/mL and postoperative PTH of 40 pg/mL stand out.

As a post-surgical complication, the patient presented transient hypoparathyroidism that was asymptomatic, with no signs on physical examination, and calcemia that decreased after receiving treatment with calcium and calcitriol.

The pathological anatomy report describes a left lower parathyroid carcinoma without invasion of adjacent tissues, of low histological grade, CD31+ immunohistochemistry, constituting a pTNM: pT3NxMx with parathyroid of preserved histomorphology adjacent to the tumor. Given the material’s fragmentation, it was impossible to certify neither the size nor the margins of the lesion.

Four months after surgery, this patient’s calcium levels returned to normal, remaining around 9.2 mg/dl with normal albumins. Consequently, the treatment for hypoparathyroidism was discontinued. PTH is maintained between 380-490 pg/mL with creatinine’s between 2.8-3.5 mg/dL, currently under clinical and paraclinical follow-up.
Discussion

Epidemiology

Data from the SEER registry, between the years 1988 to 2003, recorded 224 patients with parathyroid carcinoma [1], but this incidence has varied over the years. It is the less common endocrine neoplasia and represents only 0.005% of all cancers [3].

It can occur sporadically, but in 15% of cases, it has been associated with familial isolated primary hyperparathyroidism and hyperparathyroidism-jaw tumor syndrome [3,4]. In association with multiple endocrine neoplasia type 1 (MEN1) syndrome, it is very rare: in a series of 382 cases from the Mayo Clinic from 1977 to 2013, it was found only once [4].

Molecular pathogenesis

The main gene found in the molecular pathogenesis of parathyroid carcinoma is the HRPT2 (or CDC73) mutation. Inactivation of HRPT2 or biallelic mutation has been reported in most sporadic parathyroid carcinomas but very rarely in benign parathyroid disease [5,6].

Mutation tests for HRPT2 are not readily available, and loss of expression of parafibromin (the protein encoded by HRPT2) by immunohistochemistry is proposed as a surrogate marker for HRPT2 mutation. Tan MH et al. published a study where they showed that the loss of nuclear immunoreactivity of parafibromin has a sensitivity of 96% and a specificity of 99% in the diagnosis of definitive carcinoma. Therefore, parafibromin is a promising molecular marker for the diagnosis of carcinoma. parathyroid carcinoma [7].

Clinical picture

Parathyroid carcinoma usually presents with the signs and symptoms of hyperparathyroidism, as in the case herewith described. The average age of presentation is 46.6 years, with an equal gender distribution for women and men [2].

They can present with symptoms of severe hypercalcemia such as lethargy, confusion, stupor, and coma, although many patients with hypercalcemia have mild or no symptoms. Patients can have a markedly elevated serum calcium level—with a mean calcium concentration of 15.0 mg/dl and plasma PTH with significantly elevated levels, approximately greater than five times the upper limit of normal, as seen in this patient [8,9].

Patients with parathyroid carcinomas are more likely to present with a larger tumor at diagnosis. Symptoms arising from repercussions of hyperparathyroidism, such as nephrolithiasis and osteoporosis, may also be present initially [8]. This patient presented with altered bone mineral density and multiple microcalcifications that were thought to be related to nephrocalcinosis.

Up to a third of patients present with lymph node metastases, and a third have distant metastases, usually to the liver and bone [2,6].

Diagnosis and treatment

Parathyroid carcinoma should be suspected in a patient with primary hyperparathyroidism who presents with parathyroid crisis (or marked hypercalcemia and very high PTH levels) or a neck mass. Although preoperative localization studies help plan surgery, they do not reliably distinguish parathyroid carcinoma from adenoma [10].

Neck ultrasound and scintigraphy with 99mTc-sestamibi are the most common imaging studies used to detect benign parathyroid adenomas, but are also valuable in malignant cases [11]. Ultrasound features that suggest malignancy are large (greater than 3 cm in diameter), lobulated contours and invasion of surrounding tissues (thyroids, muscles, jugular vein). The hallmark of cervical adenopathy is infrequent, but its presence should be suspected of malignancy [6]. The scintigraphy has the advantage over ultrasound, as it objectively visualizes the location of the high-uptake gland, can target multi-glandular disease and also visualizes the mediastinum, being able to locate ectopic parathyroid tissue in some cases [6].

In case of suspicion of malignancy, higher resolution anatomical studies are of considerable value, computed tomography and nuclear magnetic resonance optimally evaluate carcinomas and parathyroid cysts [12]. Computed tomography must be requested in all patients where parathyroid carcinoma is suspected. It also allows the evaluation of deeper areas of the body and mediastinum to determine invasion of surrounding tissues.
such as the esophagus and trachea and have better anatomical references for planning the surgery [6]. Single-photon emission computed tomography (SPECT) is advantageous over flat imaging because it provides useful anatomical information, which improves overall diagnostic confidence, even though its diagnostic value in parathyroid carcinoma is still being evaluated [13-15]. The cytological study is not recommended through aspiration puncture with a fine needle as it has been shown to be not very profitable and there is a potential risk of tumor dissemination secondary to the procedure [6].

In this case, a parathyroid scintigram with SPECT-CT was performed, which confirmed increased uptake in the left parathyroid region. Although it did not reliably establish the etiological diagnosis, the atypical characteristics allowed us to identify this etiology.

The first line treatment is surgery, the only curative treatment. It is the main treatment, both for initial parathyroid carcinoma and for the treatment of recurrence or metastasis. The recommendation is the resection in bloc of the primary tumor next to the ipsilateral thyroid lobe, the presence of regional adenopathy is not common, but does exist, compartmental resection of the involvement of the nodal territory is also recommended [16]. The single resection of the parathyroid gland can be performed, but in selected cases, and requires a posterior narrow follow-up, its effectiveness not being demonstrated in the long term [16]. There is clear evidence that the in bloc resection of the primary tumor, including ipsilateral thyroid lobe, involved adjacent structures and adenopathy of being present, has advantages over parathyroidectomy that reduce the probability of recurrence of the disease by increasing the free time of illness and prolonging survival [17]. In this case, left lobectomy and left parathyroidectomy in bloc were chosen.

The definitive diagnosis is made after surgery with the pathological anatomy. Pathologic features such as a trabecular pattern, fungal figures, thick fibrous bands, and capsular and vascular invasion are highly suggestive of parathyroid carcinoma, but the two criteria for making a definitive diagnosis of parathyroid carcinoma are the local invasion of contiguous structures and metastasis. Lymphatic or distant [18,6].

Radiotherapy and chemotherapy have not demonstrated efficacy in the treatment of these tumors, which further reaffirms the surgical treatment as the only treatment option, even in the recurrence of the disease, in these cases surgery of the tumors is recommended, both cervical and mediastinal, as well as localized metastases to reduce the tumor mass and control hypercalcemia [17].

Monitoring and prognosis

Follow-up is done with measurement of serum calcium and PTH, initially after surgery, then every six months, and then annually. In addition, it is also recommended to perform a thyroid ultrasound at least once a year [19,6]. If biochemical evidence of recurrence is present, imaging tests can be performed to identify recurrence. In this case, elevated PTH persists, and we associate it with the patient’s chronic kidney disease, maintaining clinical and biochemical follow-up [20].

Regarding the prognosis, one-third of patients are cured in the initial or follow-up surgery, one-third may recur after years without disease but can be cured with a new surgery, and one-third of patients have a short and aggressive course. A 22-year prospective follow-up study by Naifa L Busaidy et al., which included 27 patients, showed that the 5-year survival was 85% and the 10-year survival was 77%. Five patients died of parathyroid carcinoma; all deaths were related to hypercalcemia [21,2,6]. Young age, female sex, diagnosis in the last year, small tumor size, and absence of distant metastases were found as good prognostic factors [22].

In summary, a 55-year-old patient with a history of multiple cardiovascular diseases and CKD is analyzed, who presents with primary hyperparathyroidism with very high serum concentrations of calcium and PTH, in whom, due to suspicion of malignancy, a left lobectomy is performed and Left parathyroidectomy with in bloc resection, whose pathological anatomy showed a parathyroid carcinoma.

Conclusions

Parathyroid carcinoma is a very rare cause of primary hyperparathyroidism. It presents symptomatically with a larger tumor and with bone and kidney repercussions. The mainstay of treatment is surgery, both as initial treatment and for treatment of recurrence or metastasis.

In a third of patients, the disease can recur. However, they can be cured with a second surgery.

Recommendations

Parathyroid carcinoma should be suspected in a patient with marked hypercalcemia and very high PTH.

Bone and kidney repercussions should be assessed initially, both by imaging bone mineral density and renal parenchyma, as well as by biochemical analysis.

When this entity is suspected, initial surgery should include parathyroidectomy or in bloc resection of the parathyroid mass, the surrounding capsule, also including ipsilateral thyroid lobectomy, and any adjacent tissue that has been invaded by the tumor.

Patients should be followed for the possibility of recurrence by measuring serum calcium and PTH and at least a thyroid ultrasound once a year.

References


