CASE STUDY

Hyperfunctional Parathyroid Carcinoma With Mediastinal Extension

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Abstract Parathyroid carcinoma (PC) is an extremely rare malignancy, of which 0.005% are of all tumours and between 0.5% and 5% of all parathyroid neoplasms. Preoperative diagnosis is often difficult and is almost always obtained only after post-surgical histopathology. The prognosis is related to the local extent of disease and to complete surgical resection of the tumour.

We report an uncommon case of hyperfunctional PC with mediastinal extension, emphasising the diagnostic difficulties, histopathological features and treatment strategies. The most recent data in the literature are analysed as well.

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PALABRAS CLAVE
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Resumen El carcinoma de paratiroides (CP) es una neoplasia maligna extremadamente rara, que constituye el 0,005% de todos los tumores y entre el 0,5 y el 5% de todas las neoplasias de las paratiroides. El diagnóstico clínico de CP es difícil y en la mayoría de los casos se realiza tras el examen histopatológico. El pronóstico está vinculado a la extensión local de la enfermedad y a la radicalidad de la extirpación quirúrgica.

Presentamos un raro caso de CP hiperfuncionante con extensión mediastínica, enfatizando las dificultades diagnósticas, las características histopatológicas, las estrategias terapéuticas, a la luz de los más recientes datos de la literatura médica.

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Introduction

Parathyroid carcinoma (PC) is an extremely rare malignant neoplasm, which represents 0.005% of all tumours and between 0.5% and 5% of all parathyroid neoplasms. It originates in the parenchymatous cells of the parathyroid glands. From a functional endocrine standpoint, PC is often hyperfunctional, although it represents less than 5% of primary
hyperparathyroidism causes. Given the rarity of this tumour, no prospective studies on its management exist; its knowledge is based both on the description of sporadic cases and on data obtained from retrospective studies. Since the first description by De Quervain in 1904 until the present day, there have been less than 400 cases of PC worldwide. A recent epidemiological study conducted in the United States between the years 2000 and 2003 estimated that the incidence of PC in the US population was 5.73 per 10 million inhabitants. Another study showed that this cancer was more prevalent in Japan compared to Western countries, considering that about 5% of patients with hyperparathyroidism presented PC. Affecting males and females equally, PC has a higher incidence between the ages of 45 and 55 years. 1-7

We present a rare case of hyperfunctional PC with intrathoracic extension, stressing its preoperative diagnostic difficulties, histopathological features and treatment strategies, in light of the latest data from the medical literature.

Clinical Case

We present the clinical case of a 76-year-old woman seen in consultation in 2007 following the onset of persistent asthenia, dysphonia and slight dysphagia associated with left laryncoceal swelling. Both a clinical examination and a videolaryngoscopy confirmed the presence of a marked hypomobility of the left hemilarynx with severe functional adductor deficit.

Following the completion of haematological studies (PTH: 1.184; Ca: 3.3) and instrumental tests (CT, FNAB, ultrasound, PET) (Fig. 1), we suspected the existence of a "hyperfunctional parathyroid adenoma" as the cause of hyperparathyroidism. We then proceeded to remove the left cervical lesion extended to the retrosternal region by cervicosternotomy, including the recurrent and mediastinal lymph nodes at the sixth level. During the surgery it was possible to preserve the left recurrent nerve, which appeared compressed by the mass but not infiltrated. Values for PTH and calcium dropped significantly in the first 24 h after the intervention (PTH: 53; Ca: 2.41), with data being confirmed 1 week (PTH: 45; Ca: 2.39) and 1 month (PTH: 32; Ca: 2.35) after the intervention. The definitive histological result was compatible with PC (Fig. 2).

Two years after surgery, the patient suffered a local recurrence (with an increase in PTH and calcium values) (PTH: 322; Ca: 3.18), which was treated with further surgery, followed by complementary radiation therapy. During that surgery it became necessary to sacrifice the recurrent nerve with consequent irreversible paralysis of the left hemilarynx. There were no changes in respiratory rate during the postoperative period.

About 15 months after the second surgery, the patient remains with normal calcium levels and without symptoms of disease.

Discussion

The clinical diagnosis of PC is often difficult and is almost always obtained, as in the present case, only after a postoperative histopathological examination. The intraoperative diagnosis of PC is unreliable because the pathologist may only raise the suspicion of malignant parathyroid neoplasm. The examination may, in fact, show atypical cytological elements (nuclear pleomorphism, increased mitoses) but not other data such as capsular and/or vascular or lymph nodal invasion that are essential for the diagnosis of PC. 8 Intraoperative macroscopic aspects of the tumour such as size over 3 cm, multilobular surface, solid consistency, presence of a thick fibrous capsule and infiltration of surrounding anatomical structures may help in the differential diagnosis between benign and malignant neoplasm. 9-11

The clinical criteria for suspicion of malignant parathyroid neoplasm are: (1) age below 55 years; (2) marked hypercalcaemia and hyperparathormonaemia (more than 10 times over the limit); (3) severe bone symptoms...
(fibrocystic osteitis in 40%–70% of cases) and kidney symptoms (nephrocalcinosis, nephrolithiasis in 30%–60% of cases); (4) recurrent laryngeal paralysis due to tumour invasion; (5) palpable cervical swelling in 30%–50% of cases.2

Imaging studies (ultrasound, CT scan, MRI, PET) are not definitive in the differential diagnosis between adenoma and parathyroid carcinoma.10 Fine needle aspiration cytology is not recommended due to both the high probability of false negatives (which may influence the surgical approach incorrectly) and to the obvious disruption of the neoplastic capsule with subsequent neoplastic spread.12,13

Even from a histopathological point of view, the differential diagnosis may not be simple. Upon microscopic examination, some PCs are almost indistinguishable from adenomas while others are totally anaplastic. The coexistence of PC with major cell hyperplasia and adenoma, sometimes present in familial forms, is not excluded. Generally, PC is grey and has a larger size compared with adenoma, a hard consistency (due to the consistent fibrous component), occasional foci of necrosis and signs of infiltration of surrounding tissues.

Just as there is no tumour staging system (TNM) for PC, no universally accepted grading system has been encoded so far. The dimensions and metastasising of PC do not actually represent parameters that may have a role in its prognosis.14 The presence of long fibrous stretches and a trabecular growth pattern is statistically more common in PC. A useful morphological criterion in diagnosis is capsular and vascular invasion, which is present in over 60% of cases. Infiltration may be limited to the capsule or may spread to surrounding soft tissues (skeletal muscle, thyroid, nervous structures) with finger-like extension through the capsular collagen fibres. Immunohistochemical tests are usually positive for cytokeratin, neuroendocrine markers and PTH. However, studies of cell cycle proteins p27, bcl-2, mdm2 and Ki-67 have found that only 30% of cases present 3 molecular phenotypes in PC different from adenoma. Therefore, these findings have established that the aforementioned proteins cannot be considered as useful markers in the differential diagnosis.15

From a genetic standpoint, the most frequent abnormality in PC is overexpression of oncogene PRAD1/cyclin D1, located on chromosome 11. It has been hypothesised that cyclin D1 inactivates the product of the retinoblastoma tumour suppressor gene (RB), thus facilitating the ontogenic process. Such overexpression is also present in 20%–40% of adenomas and 60% of hyperplasias, which would limit its value as a marker in the differential diagnosis.16,17

A somatic and germinal mutation of the HRPT2 tumour suppressor gene has been demonstrated in a high percentage of PC cases associated with inherited primitive hyperparathyroidism with mandibular tumour (hyperparathyroidism-jaw tumour syndrome, HPT-JT). This gene is located on chromosome 1q25, which encodes a protein called "parafibromin". This protein can be identified in RNA polymerase II and the PAF1 complex, and plays a fundamental role in chromatin transcription and modelling. The discovery of similar, apparently sporadic mutations in PC may be indicative of a latent HPT-JT syndrome or a phenotypic variant.18,19

The prognosis of PC is closely linked to local disease extension at the time of diagnosis, surgical radicality of the first intervention and the possibility of local relapse within the first 2 years of treatment. The last scenario may condition a decidedly ominous evolution. When the Ki-67 is more than 10%, PC has a higher risk of short term recurrence, even after radical surgical treatment.20 Percentages of 10-year survival range from 49% to 77%.4,21

Regarding secondary locations, PC metastases occur most frequently in the lungs (40%), the laterocervical lymphatic chain (30%) and the liver (10%). Other, less frequently involved areas are the bone, pleura and pericardium. In the absence of obvious signs of recurrence, the presence of metastases can be suspected in cases of persistent hypercalcaemia or in cases of progressive increase in PTH values.21,23

Surgery is the treatment of choice; block resection includes the affected parathyroid gland, the ipsilateral thyroid lobe, the lymphatic lobes of the recurrent chain and the anatomical structures infiltrated by the neoplasia, including, if necessary, the recurrent nerve. The purpose of surgery is not only oncological but also endocrine functional. In fact, the morbidity and mortality associated with PC are generally more related to various functional aspects (PTH hypersecretion and severe persistent hypercalcaemia) than to oncological aspects.5 In selected cases of distant metastases, it is possible to perform surgical treatment on the metastasis with the use of rapid intraoperative PTH doses. In patients with disease progression, palliative pharmacological therapy with bisphosphonates and calcimimetic drugs can be useful to control the symptoms of severe hypercalcaemia, despite having no influence on the prognosis of the disease. Calcimimetic drugs become fixed on calcium receptors located on the membrane of parathyroid cells, thus reducing PTH secretion. This mechanism of action has been used successfully in the case of a patient with metastatic disease.24–26 Despite being considered a radiation-resistant tumour, treatment with adjuvant radiotherapy significantly improves survival. However, the effectiveness of chemotherapy has not yet been demonstrated.27

**Conflict of Interests**

The authors have no conflicts of interest to declare.

**References**