Journal of Medical & Surgical Pathology

Cetani and Marcocci, J Med Surg Pathol 2016, 1:2
DOI: 10.4172/2472-4971.1000119

Commentary Open Access

Nonfunctioning Parathyroid Carcinoma

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Received date: March 05, 2016; **Accepted date:** April 04, 2016; **Published date:** April 10, 2016

Keywords: Primary hyperparathyroidism; Calcium metabolism; Chromogranin A; PTH; Parathyroid tumorigenesis

Introduction

Parathyroid carcinoma (PC) is a rare endocrine malignancy accounting for less than 1% of cases of primary hyperparathyroidism (PHPT) [1,2]. There is an equal sex predilection, whereas adenomas are most commonly seen in females. Patients with PC are younger than those with adenoma (50 *vs.* 60 years) and usually present with marked hypercalcemia and/or systemic manifestations, related to either hypercalcemia or increased PTH levels.

PC is usually a sporadic disease and may rarely be associated with familial PHPT, namely the hyperparathyroidism-jaw tumor syndrome (HPT-JT) and, very rarely, multiple endocrine neoplasia type 1 (MEN1) [3]. Management is primarily surgical with en bloc resection of the tumor with involved adjacent structures [4,5].

Nonfunctioning PC is extremely rare (2% of all parathyroid malignancy) [6,7] and, with the exception of one case in the setting of MEN-2A, all cases reported so far are sporadic [7,8]. The first account of nonfunctioning PC was described in 1969 by Homes et al. [9] who reported data from four patients. Twenty-eight patients with nonfunctioning PC have since been reported [7,8,10-34] including a rare case of nonfunctioning PC as the secondary primary carcinoma following breast carcinoma [33] and nonfunctioning PC metastasis to the breast [35].

The diagnosis of nonfunctioning PC is based on the finding of a carcinoma of parathyroid origin in the absence of parathyroid hyper function, normal concentrations of serum calcium and PTH.

Clinical Approach

A preoperative diagnosis for nonfunctioning PC remains a significant challenge for the clinician and may only be suspected on the basis of the location of the lesion. It is worth noting that nonfunctioning PC is diagnosed in most patients in the sixth or seventh decade (age range 27-71 years) and, due to the absence of symptoms of hyperparathyroidism, the diagnosis is made at a late stage [7,10-28,30-33]. The presenting clinical sign in most cases is a palpable neck mass which is present in about 90% of reported cases [7,10-13,15-22,25-27,31-33,36]. Other common symptoms and signs include dysphagia and choking (30%), hoarseness or vocal cord paralysis (30%) and dyspnea (30%) [7,10,13,22-27,29]. It should be pointed out that in patients with classical hypercalcemic PC the definitive diagnosis is also generally made after surgery at histology or when the disease recurs [5]. However, in the latter patients some clinical features, i.e. markedly elevated serum calcium levels [>12 mg/dl (>3 mmol/l)] and a large parathyroid lesion (>3 cm) (the so-called >3+>3 rule as suggested by Talat et al.) should raise the suspicion of a PC [37]. Because of the absence of specific features, diagnosis of nonfunctioning PC is usually always established at histology. The microscopic features are identical to those of functioning PC [38]. These tumors are rather large and mostly consist of oxyphil or clear cells and can be misdiagnosed as thyroid carcinomas such as Hürthle cell or medullary carcinoma [39]. The presence of uniform sheets of cells arranged in a lobular pattern separated by dense fibrous trabeculae, atypical mitotic figures, full thickness capsular invasion with growth into surrounding neck structures and extratumoral vascular invasion may all raise the suspicion of nonfunctioning PC [38,40]. The parathyroid origin can be confirmed by positive immunostaining for PTH, NSE, cyclin D1 and chromogranin A, and negative staining for thyroglobulin, calcitonin and thyroid transcription factor 1 [7,19,21,23,26,29-33].

At variance with other reported nonfunctioning PCs, diagnosis of a thyroid follicular nodule by fine needle aspiration cytology (FNAC) was made in the 50-year-old male patient we recently described [34]. The parathyroid nature of the lesion could not be suspected before surgery and was only incidentally discovered during a carotid doppler ultrasound scan. Neck ultrasound confirmed a 1.3 cm lesion with no evidence of enlarged lymph nodes. It is well-known that in experienced hands, neck ultrasound has a high sensitivity for recognizing an eutopic parathyroid lesion, but it may fail when the parathyroid tumor is located in an ectopic site or within the thyroid [41,42]. The latter was the case both in our patient and in the patient described by Kim et al. [43]. Of note, thyroid and parathyroid lesions may share some morphological features and therefore FNAC may fail to distinguish a parathyroid tumor from a benign thyroid nodule [44]. Indeed, colloid-like material and macrophages, which are generally found in a thyroid nodule, can also be present in a parathyroid lesion [45]. Conversely, parathyroid cells are generally smaller than thyroid cells and have less cytoplasm and more chromatin, but these are nonspecific signs [45].

On the basis of the cytological report the patient underwent right thyroidectomy. Histology showed that the tumor had a markedly irregular infiltrative growth with a trabecular pattern and invasion of the thyroid and cervical soft tissues. The parathyroid nature of the tumor was confirmed by negative immunostaining for thyroglobulin and strongly positive staining for chromogranin A and PTH. These findings are in agreement with those reported in the literature, pointing out that a definitive diagnosis of nonfunctioning PC is made on the basis of light microscopic features and the immunohistochemical profile [7,21,23,26,29-33].

It has been suggested that a decreased synthesis of PTH, production and secretion of an abnormal inactive molecule of PTH, or impaired

secretion of PTH account for the non-secreting nature of PC [15-17,21]. The latter hypothesis was supported by the evidence at electronic microscopy of an increased number of cytoplasmic organelles, as well as cytoplasmic secretory granules and occasional lipid vacuoles and glycogen [15,17]. However, these findings were not confirmed by other authors who found an increased number of mitochondria (with a reduced number and size of rough endoplasmic reticula and Golgi apparatus) and increased cytoplasmic glycogen and liposomes instead of specific secretory granules [16,21]. On the other hand, Baba et al. detected the pre-pro-PTH mRNA in a nonfunctioning PC suggesting that PTH synthesis is not always absent [46]. The immunohistochemical finding of PTH in the tumor of our patient confirms its parathyroid origin as well as its ability to transcribe the PTH mRNA.

At variance with other cases, the diagnosis of nonfunctioning PCs in our patient was made at an earlier age (50 years) with a tumor size of only 13 mm probably due to being submitted to surgery because of a follicular thyroid lesion. After surgery, serum calcium was normal and PTH levels were normal or slightly elevated. Serum chromogranin A and neuron specific enolase were in the normal range. The pre- and postoperative biochemical data are summarized in Table 1. In April 2015, on the basis of low levels of serum 25-hydroxyvitamin D concentration, the patient started vitamin D supplementation. Post-surgical imaging studies including neck ultrasound, total body computed tomography and 18FDG-PET scans were all negative for local and metastatic disease. Thus far, the patient has been followed up for 14 months without any evidence of tumor recurrence or metastasis.

Date of examination	Total serum calcium[1]	Ionized calcium[2]	Plasma PTH	25(OH)D
August 2014 (Surgery)	9.2 mg/dL	-	68 pg/mL[3]	-
October 2014	9.3 mg/dL	1.25 mmol/L	53 pg/mL[3]	36 ng/dL
April 2015	9.1 mg/dL	1.17 mmol/L	38-44 pg/mL[4]	17 ng/mL
October 2015	9.1 mg/dL	1.18 mmol/L	39 pg/mL[4]	21 ng/mL

[1] Normal range: 8.6-10.2 mg/dL

[2] Normal range: 1.13-1.32 mmol/L

[3] Normal range: 10-65 pg/mL (PTH 2end generation assay)

[4] Normal range: 8-40 pg/mL (1-84 PTH 3rd generation assay)

Table 1: Summary of biochemical data of the patient before and after surgery.

Taking into account the overall considerations, preoperative diagnosis of nonfunctioning PC is rather difficult today. In our view, nonfunctioning PC could be considered in every patient with a large neck mass regardless of serum calcium and PTH levels. Patients with suspicious nonfunctioning PC should be referred to a dedicated endocrine surgeon for an initial operation and the excised tissue should be evaluated by an experienced pathologist. Once the diagnosis has been established regular imaging monitoring is recommended.

Few data are available on the follow up of patients with nonfunctioning PC. Recurrences occur in about half of the patients [10,12,14,15,17-20,22,32]. The majority, however were still alive when reported in the literature even though the follow up was rather short; only four patients were followed for more than 5 years after initial surgery [7,35]. Information on mortality is not available but the advanced stage of PC at diagnosis predicts a poor prognosis, worse than that of patients with classical hypercalcemic PC [2,47] in whom the overall survival is about 72% and 50% at 5 and 10 years respectively [5,6,47].

Conclusions

Nonfunctioning PC is typically diagnosed at a late stage in the course of the disease because of the lack of classical symptoms of hyperparathyroidism. The presence of a palpable neck mass is the most common clinical finding. At variance with the majority of previous cases, we recently reported a rare case of nonfunctioning PC misdiagnosed prior to surgery as a follicular thyroid nodule. The possibility of a nonfunctioning PC, even though rare, should be considered in the differential diagnosis of a nodular thyroid lesion, particularly when of a large size. Histological criteria are not always sufficient for the differential diagnosis, which can definitely be established using immunohistochemistry. Thus, the clinical, pathologic and immunohistochemical picture should guide the final diagnosis.

Patients with nonfunctioning PC appear to have a poorer diagnosis than those with functioning PC because the tumors are diagnosed at a more advanced stage or possibly have more aggressive behavior.

Competing Interests

The authors declare that they have no competing interests.

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