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Parathyroid carcinoma and oxyphil parathyroid adenoma: an uncommon case of misinterpretation in clinical practice

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Abstract. A 46 year-old male presented with persistently high level of serum parathyroid hormone (PTH), despite successful resection of an oxyphilic cell parathyroid adenoma of the left lower gland. Renal function and serum calcium were normal, leading to vitamin D deficiency being considered. Tc99m-sestamibi parathyroid scintigraphy showed no capitation, but a cervical ultrasound demonstrated an increase in the lower parathyroids. Surgery confirmed that the right gland was normal but the left corresponded to parathyroid carcinoma. The patient developed severe hypocalcemia, with PTH values being consistent with hypoparathyroidism for a few months. However, a progressive increase in calcium and PTH serum levels indicated recurrence of disease. Tc99m-sestamibi scintigraphy demonstrated hyperfixation in topography of the left inferior parathyroid and the patient was subjected to a third and more extensive surgery, with removal of lymph nodes and adjacent thyroid tissue. Serum calcium and PTH remained elevated, requiring loop diuretics and intravenous bisphosphonates to control hypercalcemia. Cervical radiotherapy was implemented as adjuvant therapy. After two months the patient complained of dyspnea, and a CT scan of the chest demonstrated areas of parenchymal condensation, suggestive of actinic pneumonitis. At the 2-year follow-up no major issues were evident.

Key words: Parathyroid carcinoma, Oxyphil parathyroid adenoma, Hyperparathyroidism, Hypercalcemia

FEWER than 1% of cases of primary hyperparathyroidism are due to parathyroid carcinoma [1-7]. Nonfunctioning forms are extremely rare, with approximately 20 cases reported in the literature [8-11]. The average age of onset is 45-55 years, which differentiates it from parathyroid adenoma, which occurs predominantly in postmenopausal women [12-18]. Parathyroid carcinoma is rarely multicentered or located in the mediastinum [19-21].

Oxyphil adenomas of the parathyroid are uncommon and in the past were considered nonfunctioning [22]. However, functioning oxyphil parathyroid adenoma does occasionally occur and can mimic parathyroid carcinoma in terms of clinical features and tumor

size [23]. Warren and Morgan first described a pure functioning oxyphil parathyroid adenoma in 1935 and proposed the diagnostic criteria that are currently used: (a) at least 90% of the adenoma is composed of oxyphil cells, (b) a biopsy or excision of a second histologically normal parathyroid gland to exclude diagnosis of hyperplasia, and (c) postoperative alleviation of hypercalcemia [24].

Pre-operative diagnosis of parathyroid carcinoma is difficult. Imaging tests cannot differentiate between adenoma and carcinoma. Fine needle aspiration (FNA) is not effective, as cytological analysis is not reliable (common false-negative results) and should be avoided because of the risk of rupturing the capsule and consequent seeding of tumor cells (parathyromatosis) [25]. Macroscopically, the tumor is a large solitary firm mass (> 1.5 cm), with a fibrous grayish-white capsule that adheres to adjacent cervical tissues, with invasion of the ipsilateral thyroid lobe, cervical muscles, vessels or lymph nodes, while adenoma tend to be soft and

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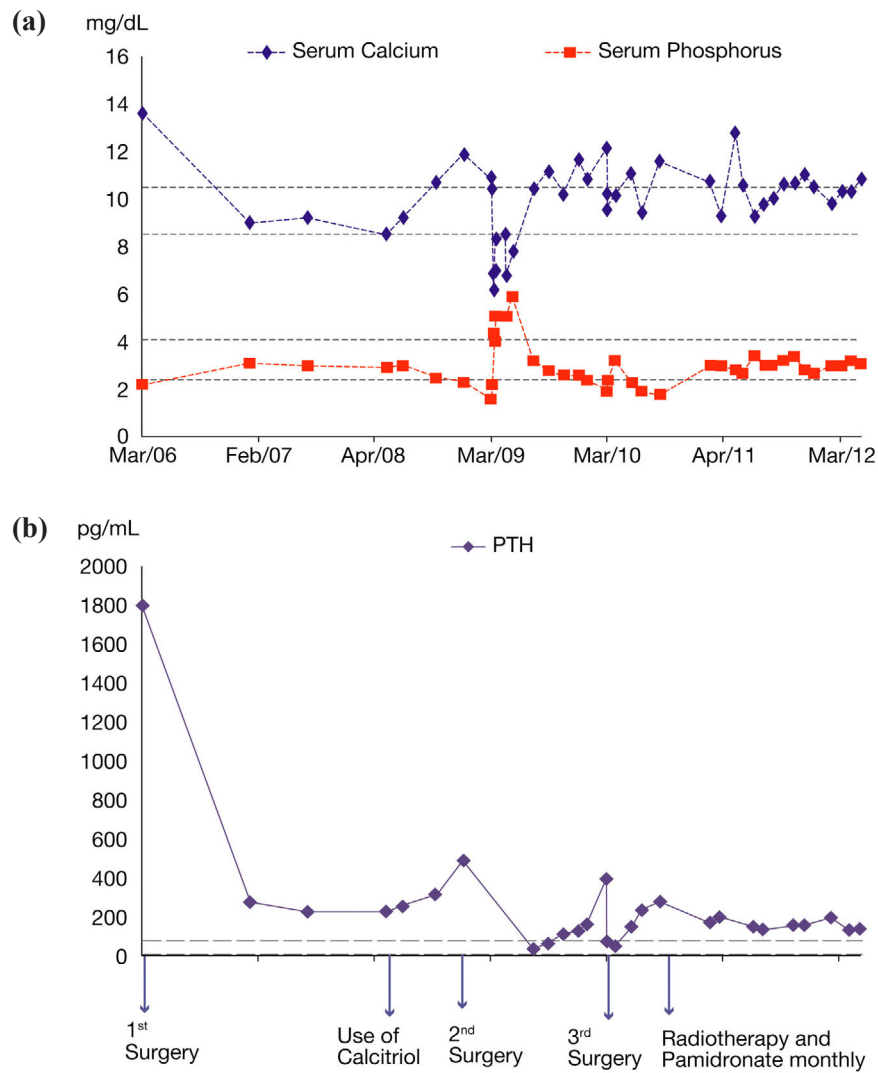


Fig. 1 Graphs of serum calcium, phosphorus (a) and parathyroid hormone (b) with the broken lines showing their minimal and maximal limits of the normality of 8.5 - 10.5 mg/dL, 2.4 - 4.1 mg/dL and 10 - 65 pg/mL, respectively.

ovoid, with a brown color and yellowish undertones [3-7, 12-18].

At the time of diagnosis, invasion to adjacent structures is common and observed in approximately 23% of the cases. Invasion normally affects the thyroid (15%) and regional lymph nodes (4%) but can occur in other organs (2%) [2-19]. With regard to distant metastases, pulmonary and liver involvement occurs in 40% and 10% of cases, respectively. However, metastases to bone, pleura, pericardium and pancreas have been reported. In cases of recurrent disease, it is advisable to perform a neck and chest CT scan and sestamibi scintigraphy [2-19].

The current report concerns a case of recurrent primary hyperparathyroidism caused by parathyroid car-

cinoma, initially identified as an oxyphil parathyroid adenoma (atypical). A literature review and discussion of the case are presented.

Case Report

A 46-year-old male was admitted to the Endocrinology Service of Clementino Fraga Filho University Hospital (HUCFF) in June 2007 with persistent hyperparathyroidism. He had a history of primary hyperparathyroidism manifested as hypercalcemia, very high serum levels of PTH (Fig. 1), bone pain and radiological evidence of osteitis fibrosa at the iliac and fifth lumbar vertebra. Furthermore, he had a history of gastric ulcer. There was no family history of primary hyperparathy-

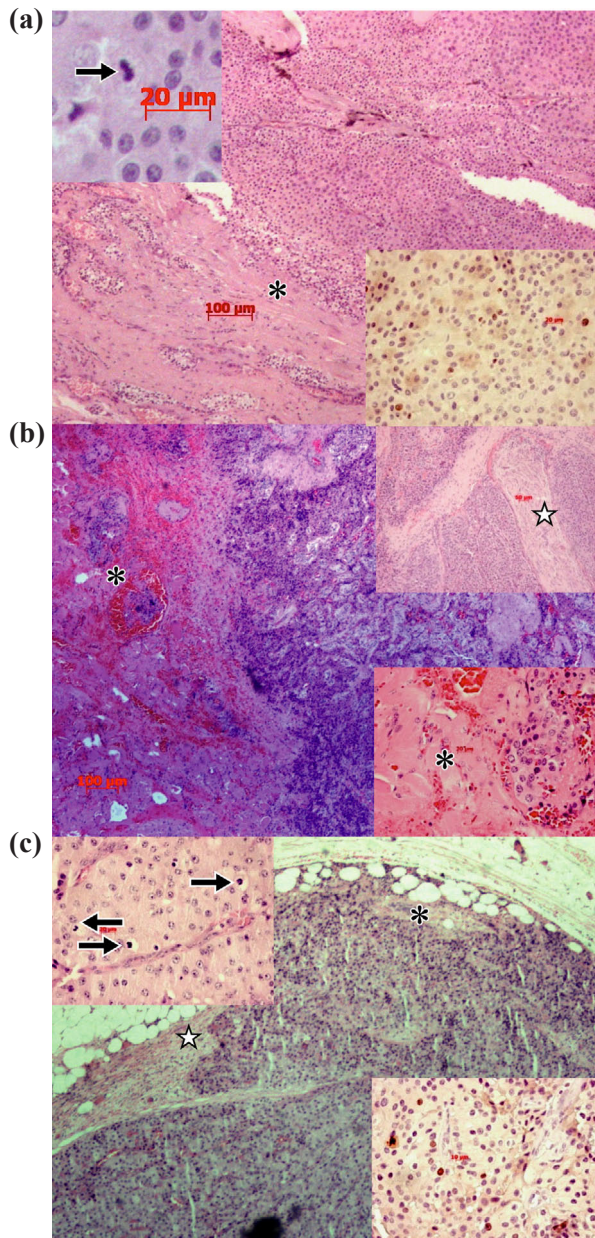


Fig. 2 Hematoxylin & Eosin stained (4x and 40x magnification) of parathyroid tissue. (a) Revised slides of the 1st surgery with thick fibrous complete capsule (asterisk). Upper left corner: HE 40x mitotic figure (arrow), mitotic rate <5/10 hpf. Lower right corner: Ki-67 (MIB-1) immunoscore of 10%. (b) Slides of the 2nd surgery with nodules of tumor cells infiltrating skeletal striated muscle (asterisk) and cervical soft tissue. Upper right corner: HE 40x tumor cells involving a thin band of neural fiber (white star). Lower right corner: HE 40x tumor cells and skeletal striated muscle (asterisk). Mitotic rate > 5/10 hpf. (c) Slides of the 3rd surgery with tumor nodules invading the capsule (white star) and adjacent fatty tissue (asterisk). Upper left corner: HE 40x mitotic figure (arrows), mitotic rate > 10/10 hpf. Lower right corner: Ki-67 immunoscore of 20%.

roidism or any other endocrine disease.

Fourteen months prior to admission the patient had an enlarged left inferior parathyroid resected in another hospital. The microscope slides were reviewed and histopathology revealed a solid parathyroid neoplasm well circumscribed and encapsulated. The cells were polygonal, with large eosinophilic granulation (oxyphil) of the cytoplasm and distinct cell membranes; the nuclei were regular, enlarged, and round with occasional pleomorphism; mitotic figures were rare with mitotic rate < 5/10 high power field (Fig. 2). Fibrosis bands were limited to the capsule and there was no vascular invasion. The initial diagnosis was an oxyphil parathyroid adenoma. During the postoperative period, serum calcium decreased markedly and the patient received oral supplements of calcium and vitamin D for several months. However, serum PTH remained elevated.

During the following months, the patient was subjected to examinations: (1) Bone mineral density (BMD) using dual-energy x-ray absorptiometry (Prodigy-GE) revealed a lower than expected bone mineral density of the lumbar spine (Z-score: -2.4, T-score: -2.7) and femoral neck (Z-score: -2.1, T-score: -2.7); (2) X-rays of the skull, mandible and hands did not identify lytic lesions; (3) Imaging tests to identify pre-operative localization of the hyperfunctioning parathyroid(s) included Tc99m-sestamibi parathyroid scintigraphy, which was negative; and ultrasound, which demonstrated solid hypoechoic nodular images at the lower poles of the thyroid (parathyroid topography), the right measuring 0.8 x 0.6 x 0.5 cm and the left measuring 1.4 x 1.1 x 1.2 cm.

Afterwards the patient underwent bilateral neck exploration and resection of each of the inferior parathyroid glands, regional fat, and thymus. The left parathyroid was enlarged and firmly adhered to the recurrent laryngeal nerve. Histopathology revealed a parathyroid carcinoma measuring 3 x 2 cm, with widely invasive fibrous bands, infiltration of adjacent soft tissues, and perineural and vascular invasion. Cells were enlarged with oxyphil cytoplasm; nuclei were regular but larger than normal, with macronucleoli and frequent mitotic figures (> 5/10 hpf) (Fig. 2). Small nodules were present in fat tissue but the right parathyroid gland and thymus had no abnormalities.

During the early postoperative period the patient developed transitory hoarseness, severe hypocalcemia that required intravenous calcium for several days, and a sharp decrease in serum PTH characterizing a transi-

tory hypoparathyroidism. Oral vitamin D and calcium citrate were necessary for several months to maintain normocalcemia. There was no response to calcium carbonate, which was associated with pantoprazol-induced hypochlorhydria. The patient had reflux esophagitis and positive *Helicobacter pylori* (confirmed on endoscopy). The progressive increase in serum PTH and calcium levels was succeeded by a gradual reduction, resulting in administration of these drugs being stopped (December 2009). Recurrence of hypercalcemic hyperparathyroidism was confirmed and a third surgery was advised. The patient underwent a videolaryngoscopy that identified left vocal fold paresis. Imaging studies concerning localization and cancer staging were performed in February 2010: Tc99m-sestamibi parathyroid scintigraphy demonstrated hyperfixation in the topography of the left inferior parathyroid; a cervical ultrasound identified a hypoechoic solid nodule measuring 0.4 cm at the same site, which was confirmed by a computed tomography scan of the neck. Chest computed tomography demonstrated benign changes, secondary to chronic obstructive pulmonary disease, while abdomen and pelvis CTs were negative.

In March 2010, the patient was subjected to *en bloc* resection of the left thyroid lobe and isthmus, the parathyroid carcinoma and cervical lymph nodes in addition to recurrent laryngeal nerve section. The surgical specimen had two hard nodules, the larger of which was 1.7 cm. Histopathology of the parathyroid tumor was similar to that described for the second surgery. Ten implants were identified in connective and fat tissues with mitotic rate > 10/10 hpf. There were lymphatic emboli and metastasis in two of five isolated lymph nodes. The recurrence of hypercalcemia after two months confirmed the requirement for more aggressive therapy.

During June 2010, the patient was subjected to radiotherapy extended to the cervical and upper thoracic region, comprising 33 sessions with 46 Gy on the total field and 16 Gy on the focal field (cervical). After three months the patient complained of dyspnea with a dry cough and persistent hoarseness; videolaryngoscopy confirmed left vocal fold paralysis and a CT scan of the chest identified areas of parenchymal condensation with air bronchogram in the upper lobes of both lungs and in the apical segment of the lower lobe of the left lung, with an appearance suggestive of actinic pneumonitis. Bronchoscopy was performed to rule out pulmonary infections including tuberculosis and fun-

gal infection. The patient was treated with a high dose of corticosteroids (prednisone) resulting in clinical improvement of the symptoms.

During follow-up, the patient presented with subclinical hypothyroidism (TSH 8.2 iU/mL, fT4 1.2 ng/dL) in June 2011 and was treated with levothyroxine 25 mcg that was increased to 50 mcg after three months because the TSH levels remained elevated.

The patient progressed without major complaints until August 2012. He used oral furosemide daily and was subjected to intravenous pamidronate each month for control of hypercalcemia. Laboratory tests demonstrated increased PTH levels that were sustained between 120-200 pg/mL, while serum calcium levels remained stable.

Discussion

This report describes a case of recurrent primary hyperparathyroidism due to parathyroid carcinoma in a male patient. Several questions require to be answered. (1) Was the diagnosis of an oxyphil parathyroid adenoma correct or was the tumor a parathyroid carcinoma from the first presentation? (2) If so, could diagnosis be suspected on the basis of the severity of bone involvement, and the calcium and PTH serum levels? (3) Did the two periods of clinical hypocalcemia after tumor resection correspond to hungry bone syndrome or to a relative hypoparathyroidism? (4) If the diagnosis of parathyroid carcinoma was suspected before the second operation, would the surgical procedure have been different? (5) Should radiotherapy and/or chemotherapy have been administered as adjuvant treatment immediately after the second parathyroidectomy to avoid tumor re-growth and a third operation? (6) What has been learned from this case that could benefit future patients with the same diagnosis (oxyphil parathyroid adenoma and parathyroid carcinoma)?

1. The majority of parathyroid carcinomas are rich in oxyphil cells, whereas adenomas are usually formed from chief cells. However, clinical and laboratory manifestations of the rare oxyphil adenoma can mimic those of carcinoma, with very large tumors and severe bone disease [23]. Furthermore, it can present with histological features of carcinomas including mitosis, fibrosis, and questionable capsular invasion. However, such cases do not demonstrate clear evidence of tumor invasion or metastasis. Furthermore, the histological diagnosis of parathyroid carcinoma has no pathogno-

monic evidence, which is based on criteria published by Schantz and Castleman in 1973 that is still valid [26-28]. These criteria include a trabecular pattern, sheets or lobules of tumor cells separated by a thick fibrous band, mitotic figures, necrosis, and capsular and blood vessel invasion [2, 26-28]. The presence of cellular atypia and a variation in cell size are not reliable diagnostic criteria for parathyroid carcinoma [2, 26-28]. However, microscopic criteria of malignancy are not always present. In this case, the presence of metastasis defines malignancy [2, 26-28]. Recently, immunohistochemistry has received much attention (negative staining for parafibromin and/or positive for the protein PGP 9.5 would be related to the malignant tumor) [26-29]. However, despite excellent specificity for the diagnosis of malignancy, negative staining for parafibromin has low sensitivity [26-29]. Another difficulty is that it requires an accurate technique for its realization. In a study published in 2009, Howell *et al.* suggested that positive staining for PGP 9.5 could be the complement of parafibromin, increasing sensitivity without sacrificing specificity [26]. This suggests that immunohistochemistry could be used for patients with histological diagnosis of atypical adenoma to diagnose those with greater malignant potential [26-29].

Evaluating the case reported herein, we identified that the first specimen exhibited two features associated with malignancy (intratumoral fibrous bands and diffuse monotonous cells with high nuclear-cytoplasmic ratio), but lacked the absolute criteria of malignant invasion into surrounding tissues and metastasis (regional or distant). According to morphological criteria, this lesion could have been referred to as an atypical adenoma, which is a neoplasm of uncertain malignant potential that presents with few features associated with malignancy. This is not a clinicopathological entity, but such findings confirm that regular follow-up and monitoring of serum calcium levels is required. The follow-up of this patient strongly suggests that from the outset the tumor was a carcinoma.

2. Osteitis fibrosa is a common presentation of primary hyperparathyroidism in Brazil, predominantly due to delayed diagnosis, as calcium levels are not normally included in routine exams [30]. In countries where laboratory assessment of calcium, phosphorus and PTH is routinely adopted, the majority of cases are identified as asymptomatic or oligosymptomatic hyperparathyroidism [31]. Another explanation for the severe bone disease would be concomitant vitamin D deficiency,

frequently detected despite Brazil's latitude [32, 33] and eventually aggravated by the increased renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D induced by chronic PTH overproduction [34, 35]. Although 25-hydroxyvitamin D was not measured, the long period of normocalcemic hyperparathyroidism between the first and the second parathyroidectomies, can indicate vitamin D deficiency. This would be consistent with the absence of severe hypercalcemia despite very high levels of PTH. However, PTH levels of approximately 2,000 pg/mL evident in this case would justify a diagnosis of osteitis fibrosa. According to the literature, diagnosis of parathyroid carcinoma must be based on the concurrence of the following evidence: concomitant renal and bone disease, palpable neck mass, increased tumor weight (>1.9 g), elevated serum calcium levels (between 14-16 mg / dL) and elevated PTH levels (> 500 pg/mL and often > 1000 pg/mL) [34-36]. Therefore, although data from the patient were not conclusive for a malignancy *per se*, elevated PTH levels should have led to the hypothesis that parathyroid carcinoma was the cause of the primary hyperparathyroidism.

3. On two occasions the patient manifested hypocalcemia. Hungry bone syndrome was expected to occur owing to the severity of bone involvement, leading to a decrease in serum calcium and phosphorus levels [37-39]. However, after the second parathyroidectomy, there was a sharp decrease in PTH levels associated with hypocalcemia and a slight augmentation of serum phosphate levels. This suggests a transitory hypoparathyroidism, as the normal parathyroids were suppressed.

4. Had the diagnosis of parathyroid carcinoma been suspected before the second operation the surgical procedure would have been different. It would have been more extensive to guarantee extirpation of the whole tumor. The best treatment for parathyroid carcinoma is early total extirpation of the tumor and circumjacent tissues [2-18]. Surgeons should perform *en bloc* resection (ipsilateral thyroid lobe, adjacent musculature, paratracheal lymphatic tissue [Level VI] and, if involved, the thymus), as this has much influence on the prognosis and the rate of local recurrence [2-18]. Nevertheless, this is a tumor with a high rate of local recurrence and successful cure after relapse is rare. Special care should be taken to avoid disruption of the tumor capsule during resection to avoid seeding of the cells. A priority should concern controlling preoperative levels of cal-

cium with intravenous hydration, diuretics and intravenous bisphosphonates [2-18]. Furthermore, care must be taken during the postoperative period because there is a greater risk of hungry bone syndrome.

5. Parathyroid carcinoma recurrence is suspected when serum calcium rises. Complications and death are predominantly due to hypercalcemia and not local invasion or distant metastasis. The decision for adjuvant therapy usually concerns hypercalcemia and it is important to emphasize that this patient maintained normal calcium levels after the surgical procedures, particularly after the second intervention [2-18]. When recurrence is evident, a new surgical resection is recommended, as in the case reported here. In advanced cases, when the disease becomes widespread and surgical resection is not effective, the therapeutic goal is to control hypercalcemia. This can be achieved using bisphosphonates and calcimimetic agents [2-18, 40]. Although not well defined, adjuvant radiotherapy appears to reduce the rate of local recurrence and increase disease-free survival, particularly in high-risk patients, even metastatic cases [2-18]. The rarity of this disease makes it difficult to carry out randomized studies that prove the real benefit of radiotherapy. Therefore, this patient was not referred for radiotherapy after diagnosis of carcinoma. Chemotherapy has

demonstrated variable and disappointing results. The prognosis of parathyroid carcinoma is extremely variable, depending on early diagnosis and success of the initial surgical procedure. Published data suggest that tumors without major invasion sites are likely to result in patients having a longer disease-free period [2-18]. Tumor size has no impact on prognosis and lymph nodes are rarely involved, with a questionable impact on prognosis [2-18]. In this case, actinic pneumonia was a complication, but radiotherapy appeared to be effective in controlling tumor growth during the two years of follow-up.

Conclusion

This case report has demonstrated that we should always consider patients with severe forms of primary hyperparathyroidism, very high levels of PTH and clinical compotential cases of parathyroid carcinoma. Furthermore, it will aid in identifying and treating the disease in a more timely and adequate manner.

Conflict of Interest

All authors have no conflicts of interest.

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