Primary hyperparathyroidism secondary to parathyroid carcinoma

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Abstract

The authors describe a case of parathyroid carcinoma in a 40 years old man, who presented clinical symptoms evolving for six months, characterized by generalized bone pain, muscle weakness, polydipsia, polyuria, marked lassitude and a palpable cervical nodule. Laboratory results revealed severe hypercalcemia, raised alkaline phosphatase, renal failure and extremely high levels of intact parathyroid hormone (PTHi). Radiological imaging revealed the existence of osteitis fibrosa cystica and parenchymal calcification of renal tissue. Studies of the neck showed a heterogenous structure in the left lobe of the thyroid.

Following surgical excision of the tumor complete remission of clinical symptoms, as well as normalization of laboratory values were observed. Nevertheless, 10 months after surgery a new rise in PTHi level, consequent hypercalcaemia and cervical adenopathy occurred, requiring surgical removal once again. The authors present the clinical case as well as therapeutic strategies.

Keywords: hypercalcaemia, hyperparathyroidism, carcinoma.

Introduction

Primary hyperparathyroidism is a disease that has been diagnosed with greater frequency since the determination of calcaemia became a routine analysis, and the determination of intact parathyroid hormone is easy to accomplish.[1]

Parathyroid carcinoma is an extremely rare entity, corresponding to only 0.5% to 4% of all parathyroid pathologies recorded by the main institutions. For this reason, individual and institutional experience with this type of pathology is scarce, therapeutic strategies are varied, and the results are not always positive.[2-5]

Not much is known about the natural history of parathyroid carcinoma; however, it is known that its evolution is slow. Its incidence seems to be equal across genders, although non-malignant hyperparathyroidism is more frequent in females.

The clinical and laboratory presentation is similar to that of the benign parathyroid diseases, making the differential diagnosis difficult. Nevertheless, carcinoma should be strongly suspected in patients with primary hyperparathyroidism and palpable cervical mass, severe hypercalcemia (greater than or equal to 14 mg/100 ml), parathyroid hormone levels at least twice the normal range, and significant metabolic complications.[6]

A case of parathyroid carcinoma that was manifested through a condition of hyperparathyroidism is presented in this article.

Clinical case

In June 1993, a 40-year old female patient from a gypsy ethnic group began to experience clinical symptoms characterized by: postprandial infarction, nausea, vomiting, non-quantified weight increase, palpitations, asthenia, anorexia, polyuria, polydipsia, generalized bone pain that was more intense in the lower limbs, and decreased muscle strength in the lower limbs.

In November, she was diagnosed with high blood pressure. During this period, the patient was admitted several times to the local hospital where corticosteroid therapy was prescribed. The patient was discharged at her own request, and in January 1994 she came to the Emergency Department of Centro Hospitalar de Coimbra.

Personal history includes adenosis, endometrial cancer and multinodular goiter (diagnosed at another institution).

Physical examination revealed: depressive posture, Cushingoid appearance with acne, and goiter. Palpa-

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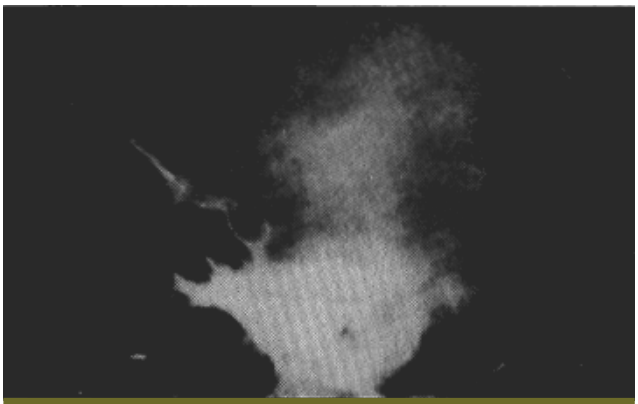
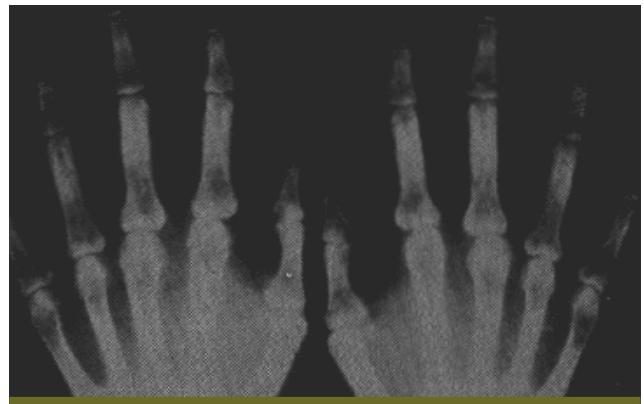


Lesions with a "salt and pepper" appearance.

FIG. 1



Images of subperiosteal reabsorption.

FIG. 2

tion revealed increased thyroid gland with a painless nodular formation in the left upper lobe with diameter of around 1.5 cm, little mobility and adhering to the deep tissues. Decreased muscular strength in the lower limbs (degree 4/5) was observed, and mild to moderate high blood pressure.

Additional tests revealed: normocytic normochromic anaemia (Hb 10,5; RBC 3,79; MGV 86,6; Htc 32,8); hyperglycaemia (155 mg/dL), mild renal insufficiency (128 *mol/L; urea 65 mmol/L), hypercalcemia (3.4 mEq/L=14 mg/dL), hypokalaemia (2.9 mEq/L), high alkaline phosphatase [1910 IU/L (NV: 37-123)] without analytical evidence of cholestasis and mixed dyslipidaemia (cholesterol 279 mg/dL; triglycerides 225 mg/dL; HDL 35 mg/dL; LDL 199 mg/dL); ionogram of the urine [Na 56 mmol/L; K 14,6 mmol/L; Ca 2,65 mmol/L (12 mmol/24h)]; summary urinalysis with low density (1010), without other changes. Serum and urinary protein analysis did not show evidence of a monoclonal peak. Thyroid tests [T3 94.4 ng/dL (NR: 86-187); T4 5.8 ng/dL (NR: 4.5-12.5). TSH 0.93 mIU/L (NR: 0.3-5.0)]. Normal vanillylmandelic acid in urine over a 24-hour period [8.98 mg/24h (NV <10)] and SACE (24 U/L). Intact parathyroid hormone 1638.6 pg/mL (NR: 12-72 pg/mL).

ECG: sinus tachycardia of 115/min without other significant changes. X-ray study revealed skull lesions with a 'salt and pepper' appearance (*Fig. 1*), calcifications of the renal areas and subperiosteal reabsorption of the second phalange of the 2nd, 3rd and 4th fingers of both hands (*Fig. 2*).

Abdominal and renal echogram: slightly increased liver without any significant changes in its echostructure, but with a shiny appearance, probably related to steatosis. Vesicular lithiasis. Kidneys with dimensions, morphology and echostructure within normal parameters; right and left kidneys with images suggestive of stones. Thyroid echogram: hypoechoic, heterogeneous and irregular nodule on the posterior side of the left thyroid lobe of around 3.8 cm in diameter; a small, less echoic nodule formation in the upper one-third of the right lobe of the thyroid; next to the left internal jugular vein, another nodule formation of 1.6 cm diameter was observed (adenopathy?).

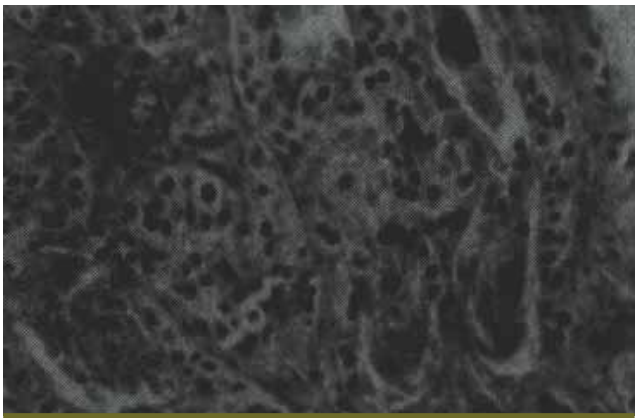
CAT scan of the neck: heterogeneous liquid-type formation of around 2.22 cm in the transverse diameter, heterogeneously accentuated with IV contrast, situated on the posterior side of the left thyroid lobe. In the same area, next to the outer side of the internal jugular vein, we observed a nodule of around 1 cm diameter, the margins of which were clearly visible with the IV contrast (adenopathy) (*Fig. 3*).

During hospitalization, and despite the therapy given for hydro electrolytic disequilibrium, there was no change in the clinical symptoms and laboratory tests. On day 14 of hospitalization, the patient underwent a parathyroidectomy of the left upper gland with thyroid lobectomy of the left lobe, and isthmectomy, contralateral subtotal lobectomy and excision of two adenopathies of the left internal jugular chain.

There were no complications in the perioperative period, except for a single episode of symptomatic hypocalcaemia on day four. An anatomical-pathological

Heterogeneous nodule formation in the left thyroid lobe.

FIG. 3



Histology.

FIG. 4

study of the surgical specimen revealed: "Parathyroid carcinoma continuously invading the thyroid gland, presence of vascular invasion and areas with necrosis. Lesions with nodular hyperplasia and two ganglia with tumor metastases".

On discharge, the patient was clinically well and was receiving oral calcium (2000 mg/day), calcitriol, ferrous sulphate and enalapril.

After regular outpatient follow-up, the therapy was suspended once the biochemical parameters were within the normal range. The patient continued with a good overall condition, asymptomatic, and without any sign suggestive of tumor relapse, but in October 1994, high levels of intact PTH were detected (112 pg/ml), with normal calcaemia. A CAT scan of the cervix did not show any images suggestive of recurrence of the tumor.

In May 1995, hypercalcemia (2.80 mEq/l) and high levels of intact PTH (174 pg/ml) were detected; also, the asthenia, localized bone pain in the lower limbs and muscular weakness returned. CAT scan of the cervix was performed, and again no signs of recurrence of the tumor were observed.

In October 1995, a small left supraclavicular adenopathy of the cervix was detected, leading to a new tomodensitometry that revealed an image of a left supraclavicular nodule suggestive of metastatic adenopathy.

In November 1995, the patient underwent modified radical cervical dissection on the left side, and an anatomical-pathological study confirmed the presence of ganglion metastasis of parathyroid carcinoma. The patient showed clinical and laboratory improvement; nevertheless, complete normalization of the levels of calcaemia and parathyroid hormones was not possible.

The patient is in follow-up in outpatient consultations with clinical and laboratory monitoring, and local relapse or distant metastasis is no longer observed in the imaging tests.

Discussion

In the majority of cases, primary hyperparathyroidism is due to a parathyroid adenoma, and less frequently to hyperplasia of the four glands; it is sometimes associated with multiple endocrine neoplasia (MEN). In rare instances, they are caused by a carcinoma.[7-9] In a patient aged under forty years with severe hyperparathyroidism, the probability of parathyroid carcinoma should be taken into consideration.[4]

The typical symptoms of hyperparathyroidism consist of diffuse bone and joint pain, gastrointestinal and neuropsychiatric symptoms, and kidney cramps; however, all these symptoms are rarely found together in the same patient.[7,10,11]

The majority of cases show changes in tubular reabsorption, evidence of nephrocalcinosis, renal insufficiency, chondrocalcinosis, periarticular calcifications and fractures secondary to diffuse osteoporosis - these may be the first manifestation of hyperparathyroidism.[12,14] Most of these clinical manifestations are a direct consequence of hypercalcemia. Any skeletal changes observed are due to osteoclast activity caused by excessive parathyroid hormone, resulting in

diffuse osteopenia and characteristic subperiosteal erosions.[14,15]

High blood pressure is common in primary hyperparathyroidism, and is not considered a consequence of this condition, since the incidence of high blood pressure in these patients is identical to that of the general population.[12,16,17]

In our case, the clinical characteristics of hyperparathyroidism were very evident, and were confirmed by laboratory and radiological findings. The suspicion of parathyroid carcinoma was due to the coexistence of severe hypercalcemia, a palpable cervical mass, and very high serum levels of parathyroid hormone. The presence of Cushingoid appearance and hyperglycaemia is explained by the corticosteroid therapy that was previously administered. Additional tests enabled us to rule out the hypothesis of MEN.

Where parathyroid carcinoma is not suspected, which is often the case, an open biopsy can be performed. In cases where a carcinoma is present, the consequence of this procedure is disastrous, with inevitable local dissemination of the carcinomatous cells.[6] An appropriate en bloc resection of the tumor, avoiding rupturing the tumor capsule, can cure some patients.[5,24,25] The diagnosis was confirmed by an anatomical-pathological analysis of the specimen.

The histological characteristics of parathyroid carcinoma include: capsular and vascular invasion, cells that are generally organized and separated by fine fibrous trabeculae, and the presence of cell mitoses in most cases (*Fig. 4*). [2,4,18,19]

The disease metastasized to the regional lymph nodes in advanced clinical cases, and distant metastasis can be found in the lungs, liver and bones, in decreasing order of frequency.[6]

The therapeutic option was en bloc resection of the affected parathyroid glands, taking care to maintain capsular integrity. Long periods free of disease are described with this therapy. Chemotherapy and radiation are almost always ineffective treatments.[6,20,21] Repeated resections of local or distant metastases are clearly beneficial, either for mitigation of symptoms or improvement of the biochemical disequilibrium, thereby reducing the risks of metabolic complications.[6] Unfortunately, this surgery is palliative and once recurrence is observed, the disease will continue to recur.[6]

Recurrent disease means the return of the hypercalcemia after at least six months of normocalcemia.[22,23] Tumor relapses usually occur between six months to three years after the initial surgical procedure, metastatic implants being the most common,[6] resulting in higher serum levels of parathyroid hormone and calcium. The survival time after diagnosis is around seven to eight years.[6] ■

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