

Association between atypical parathyroid adenoma and neurofibromatosis

^{1,2,5}Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (FCM-Unicamp), Campinas, SP, Brasil

³Departamento de Anatomia Patológica, FCM-Unicamp, Campinas, SP, Brasil

⁴Departamento de Radiologia, FCM-Unicamp, Campinas, SP, Brasil

Aline Mesquita Ferreira de Favere¹, Daniela Miti Tsukumo², Patrícia Sabino de Matos³, Sérgio Luiz Marques dos Santos⁴, Cristina Alba Lalli⁵

Correspondence to:

Aline Mesquita Ferreira de Favere
Universidade Estadual de Campinas,
Departamento de Clínica Médica
Rua Tessália Vieira Camargo, 126
Cidade Universitária "Zeferino Vaz"
13083-887 – Campinas, SP, Brasil
lininha_mfe@hotmail.com

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SUMMARY

Primary hyperparathyroidism is a disease characterized by excessive production of parathyroid hormone (PTH), which is due to a parathyroid adenoma in 85% of cases. An atypical parathyroid adenoma, with some histopathological features of parathyroid carcinoma, may be found in some of the cases, although it may not fulfill all the criteria for this diagnosis. Neurofibromatosis type 1 (NF1) is an autosomal dominant systemic disease that may be associated with hyperparathyroidism. We report here the rare combination of a patient with NF1 and clinical manifestations of hyperparathyroidism due to an atypical parathyroid adenoma. *Arch Endocrinol Metab.* 2015;59(5):460-5

INTRODUCTION

Primary hyperparathyroidism is a disease characterized by excessive production of parathyroid hormone (PTH) (1), which is due to a parathyroid adenoma in 80 to 85% of the cases, or gland hyperplasia in 15 to 20% of them (2,3). Less than 0.5% of the cases are due to parathyroid carcinomas (1). In some cases, parathyroid tumors may show some histological characteristics of parathyroid cancer, but they may not be enough to establish this diagnosis. These tumors are called atypical parathyroid adenomas (3).

Primary hyperparathyroidism is the third most common endocrine disease. Prevalence depends on the population studied and the detection methods used (4), and women between 55 and 75 are the most common individuals affected by the disease. In relation to clinical presentation, most individuals are asymptomatic and hypercalcemia is evidenced in routine exams. Other cases may present asthenia, nephrolithiasis, osteoporosis, and bone fractures (2). Psychiatric changes, such as depression, dementia, confusion, and stupor, may also be found (4).

Parathyroidectomy is recommended in all cases of symptomatic hyperparathyroidism. In asymptomatic hyperparathyroidism, surgery is indicated in the following cases: a) serum calcium 1mg/dL above of the nor-

mal range; b) bone densitometry T-score < -2.5 in lumbar spine, neck of the femur, total hip, or distal third of the radius and/or vertebral fracture in radiography, computed tomography (CT), magnetic resonance imaging (MRI) or vertebral fracture assessment (VFA); c) creatinine clearance < 60 mL/min or urinary calcium > 400 mg/day, and increased risk of lithiasis, or presence of nephrolithiasis or nephrocalcinosis in radiography, CT or ultrasound; d) age < 50 years old (5).

In cases of slight hypercalcemia (serum calcium < 12 mg/dL) surgery may be carried out without pre-surgical preparation. Patients with higher serum levels should receive an infusion of saline solution, diuretics, and bisphosphonates by intravenous route or calcimimetics (cinacalcet) as pre-surgical treatment, in order to reduce calcium serum levels and the risks of complications associated with severe hypercalcemia, which include hypovolemia, acid-base imbalances, and cardiac arrhythmia (2).

NF1 is a rare autosomal dominant disease whose incidence is estimated in 1 to 3,000/3,500 live births. It is caused by a mutation in *NF1* gene, which was mapped and cloned in the pericentromeric region of the chromosome 17q11.2. Its product is neurofibrin (6), a protein activates GTPase and is able to negatively regulate the proto-oncogene p21-ras. Loss of function

may lead to uncontrolled cell growth and formation of benign and malignant tumors (7). Besides, there is a known association between NF1 and autoimmune diseases, such as systemic lupus erythematosus, systemic sclerosis, and membranous glomerulonephritis (8,9).

Clinical characteristics of NF1 include *café au lait* spots and multiple cutaneous neurofibromas. Diagnosis is based on the presence of two or more of the following findings: Six or more *café au lait* spots larger than 5 mm in diameter in pre-pubescent patients, or larger than 15mm in post-pubescent patients; two or more neurofibromas of any kind, or one plexiform neurofibroma; axillary or inguinal ephelides; optic glioma; two or more Lisch nodules in the iris; distinct bone lesions such as sphenoid dysplasia, or long bones with or without pseudarthrosis; first degree relative with neurofibromatosis (10).

Patients with NF1 have increased risk of developing endocrine tumors. Pheochromocytoma is found in 0.1 to 6% of the patients with NF1 (11), and is considered a malignant neoplasm in 5 to 13% of the cases; mortality may be greater than 50% in five years (12). We also found in the literature some cases of NF1 associated with multiple endocrine neoplasia (MEN), particularly type 2 (MEN 2), an autosomal dominant syndrome that consists of medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism (6).

The objective of the present report is to describe the case of association between primary hyperparathyroidism due to atypical parathyroid adenoma and NF1.

CASE REPORT

The patient was a black woman, 62 years of age, who was referred to us due to a complaint of diffuse bone pain, asthenia, and weight loss of 10 kg in two years. She denied previous diagnosis of systemic arterial hypertension, or paroxysmal hypertensive events. In the physical examination, she showed to be in good general status, hydrated, pale mucous membranes 2+/4+, had normal blood pressure, and depressed mood. Palpation of the abdomen showed, in the right flank, a painful mass of fibroelastic consistency measuring about 7 cm in diameter, and a subcutaneous nodule located in the right hypochondrium, measuring 4 x 3 cm, also of fibroelastic consistency. Thorax examination showed pronounced kyphosis with normal lung auscultation. Skin examination showed twelve *café au lait* spots in thorax, abdomen, and upper limbs, ranging from 2 x

2 cm to 6 x 9 cm, as well as multiple popular, and nodular lesions, with some pedunculated lesions suggestive of neurofibromas, mainly on the face, thorax and abdomen. No changes were observed in any of the other systems. Laboratory tests showed serum calcium of 13.5 mEq/L, ionized calcium of 1.92 mmol/L, and PTH of 1,933 pg/mL (Table 1). Radiographic examination of long bones and skull showed lesions suggestive of brown tumor in femur and tibia, and suggested diffuse osteopenia (Figure 1). Abdominal MRI evidences extraperitoneal cystic lesions suggestive of neurofibromas, and a lytic expansile lesion in the iliac bone, without other tumors (Figure 2). Cervical ultrasound showed a nodule in the parathyroid measuring 4,5 x 4.0 x 3.3 cm. Sestamibi-99mTc scintigraphy of the parathyroid showed a nodule of 4.3 x 3.7 cm in the inferior part of the right thyroid lobe. Hypercalcemia and PTH elevation added to the imaging findings and led to the diagnosis of primary hyperparathyroidism due to parathyroid tumor. No clinical evidence, nor any of the imaging tests, suggested the presence of pheochromocytoma. NF1 diagnosis was clinically confirmed by the presence of *café au lait* spots greater than 15mm, and cutaneous neurofibromas. Excision of the subcutaneous nodule found in the right hypochondrium followed by histopathological analysis showed a neurofibroma.

The following measures were initially determined to control hypercalcemia: hydration with saline solution 0.9%; furosemide and zoledronic acid administration by intravenous route. Later on, the patient underwent parathyroidectomy, and a 83% drop in PTH was observed 10 minutes after tumor resection, compared with immediate pre-surgical PTH. Histopathological examination was compatible with atypical parathyroid adenoma (Figure 3). In spite of the focal areas of capsule irregularities with nodular tissue trapped in the normal capsule, unequivocal capsule invasion, vascu-

Table 1. Laboratory tests

Tests and reference values	Basal 12/04/2012	Follow-up 02/17/2014
Ca ²⁺ (1.15 – 1.29 mmol/L)	1.92	1.16
Ca (8.8 – 10.2 mEq/L)	13.5	9.5
Pi (2.5 – 4.8 mEq/L)	2.0	2.6
Mg (1.3 – 1.9 mEq/L)	0.69	1.9
Albumin (3.5 – 5.2 g/dL)	3.38	3.7
PTH (15 – 65 pg/mL)	1933	132
Creatinine (< 0.9 mg/dL)	0.77	0.67

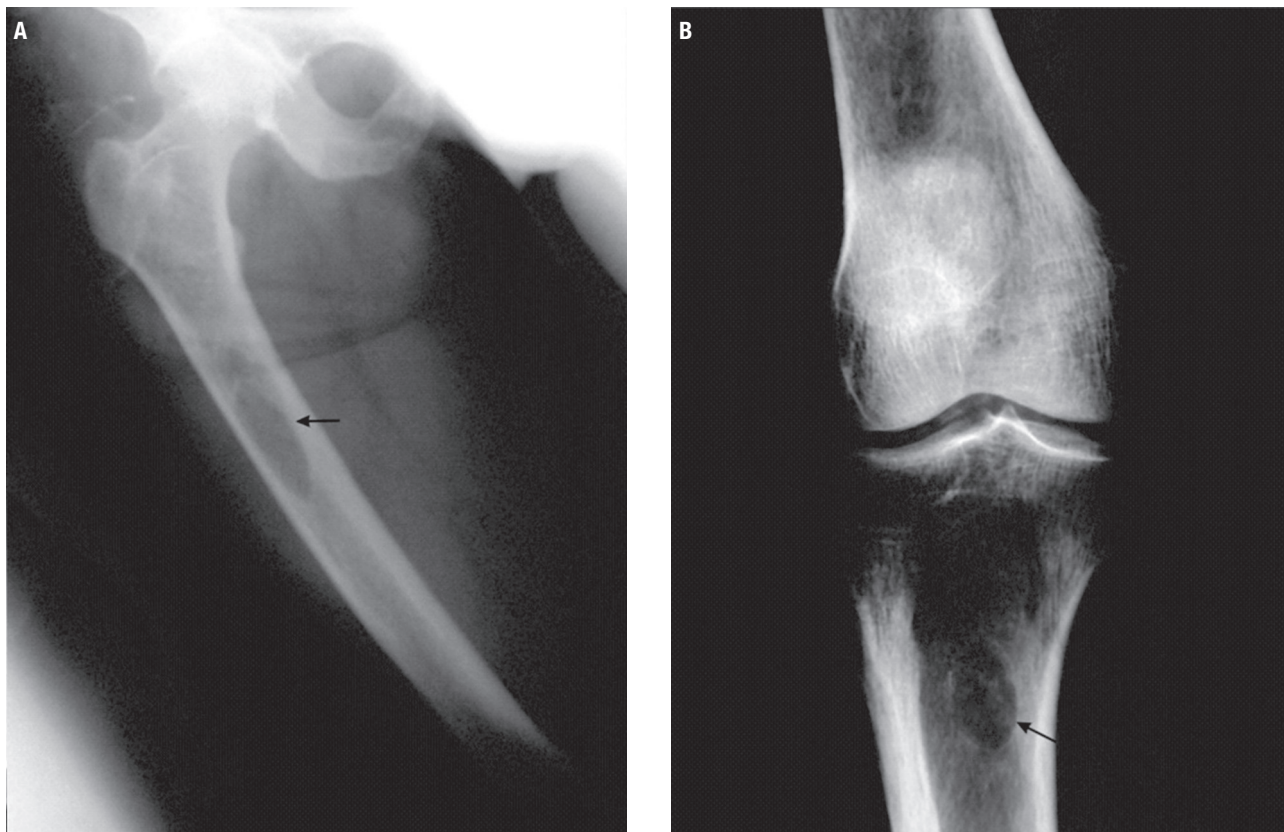


Figure 1. (A) Osteopenia and osteolytic lesion in the upper third of the tibia; (B) Osteolytic lesion in the upper third of the right femur.

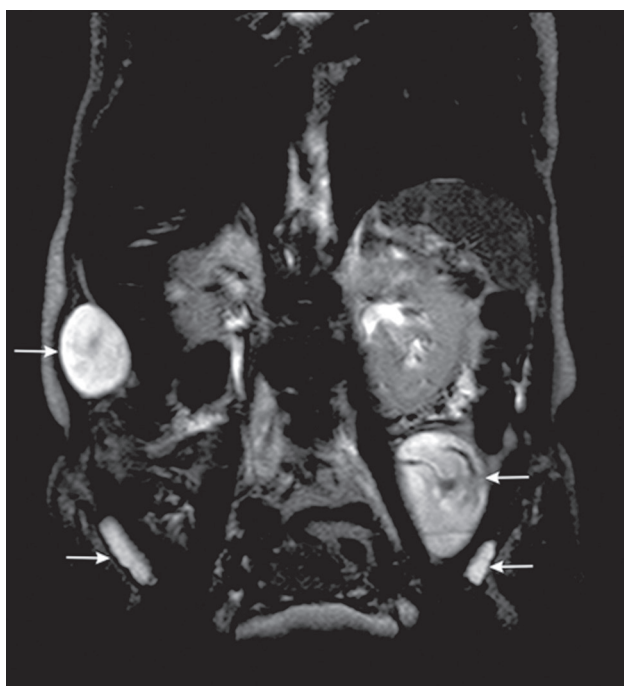


Figure 2. T2N Coronal section of the abdomen showing cystic lesions suggestive of intra-abdominal neurofibromas and bone lesions in iliac bones, more evident to the right (brown tumor).

lar and perineural, invasion of the adjacent tissue, high mitotic activity or large bands of fibrosis were not observed. Specific immunohistochemical staining showed low positivity for Ki-67 (< 1%), negative results for p53, focal areas of positivity for bcl-2, and positive results for cycline-D1 lower than 15%. These changes corroborated the diagnosis of atypical parathyroid adenoma (Figure 3).

DISCUSSION

The differentiation of parathyroid adenoma and carcinoma based on their clinical and histopathological has been a challenge. In macroscopic analysis, carcinoma is surrounded by a fibrotic capsule, and may be adhered to adjacent tissues, being locally advanced and showing distant metastases. Histopathological analysis shows trabecular growth, fibrotic tissue, mitosis figures and capsular, vascular and/or lymph node invasion (13,14).

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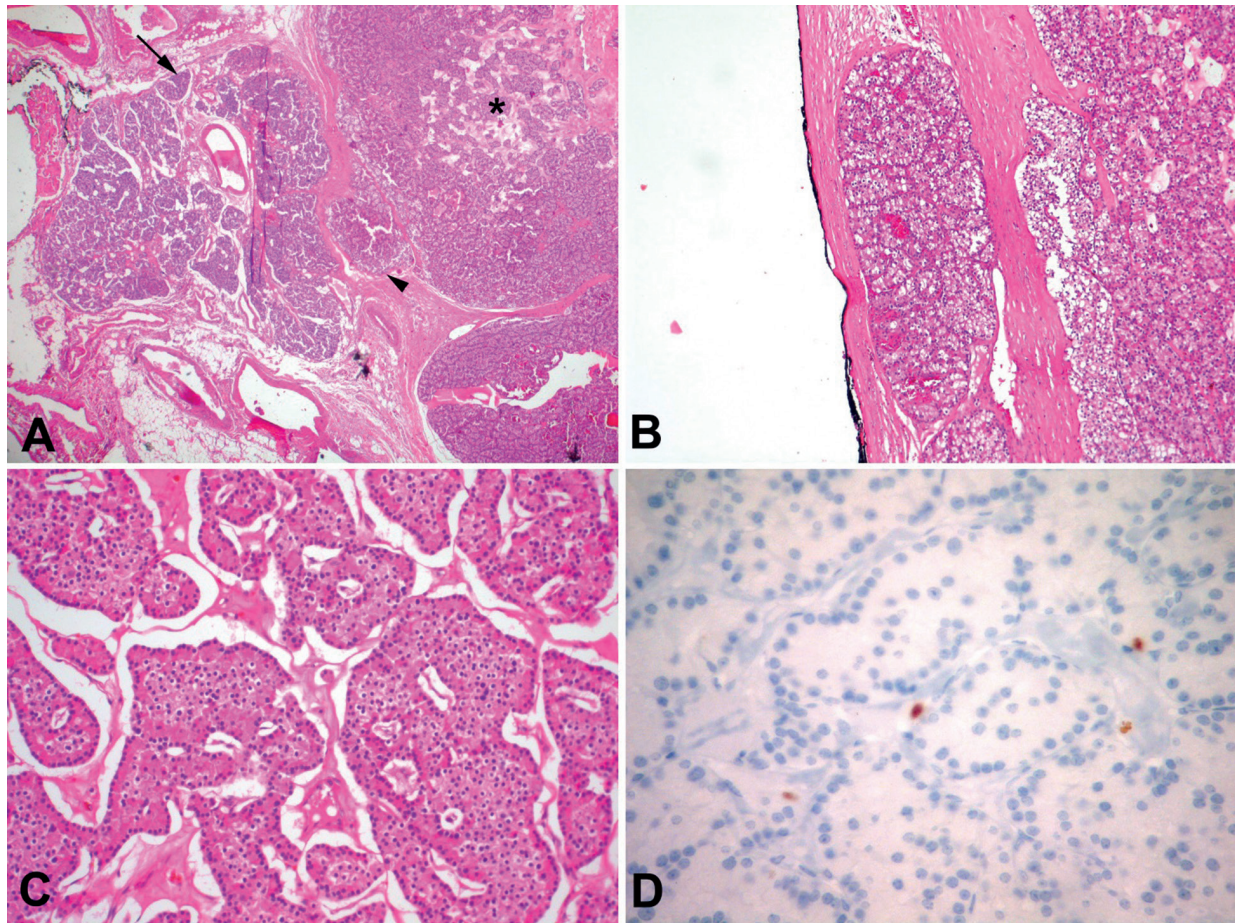


Figure 3. (A) Atypical parathyroid adenoma. Normal parathyroid tissue (arrow) is seen next to the neoplasm, which shows irregular capsule (arrowhead). Solid trabecular and glandular pattern inside of the nodule may be observed (*). (HE-100x). (B) Detail of the capsule showing islands of neoplastic tissue trapped in the fibrous capsule. (HE-200x). (C) Trabecular pattern made up of polygonal cells with ovoid nuclei, discrete atypia, and acidophilic cytoplasm (HE- 10x). (D) Low positivity (1%) for Ki-67. (IMH-400x).

According to the histopathological classification of the World Health Organization, atypical parathyroid adenoma is defined as a parathyroid tumor that do not show locally advanced growth or metastases. However, it may show cell atypia, fibrotic tissue, trabecular growth, fibrotic capsular involvement, and increased mitotic rate (15).

Clinical and laboratory characteristics are not enough to differentiate carcinomas from adenomas. The presence of a palpable mass and hoarse voice are findings that are almost exclusive of parathyroid cancer, as well as calcium plasma levels greater than 14 mg/dL, and PTH greater than 500 ng/mL (3,14).

A retrospective study carried out by University of California, whose objective was to determine clinical and histological differences between parathyroid carcinoma, atypical parathyroid adenoma, and parathyromatosis, found plasma calcium levels greater than 14

mg/dL in 16 of the 26 patients with carcinoma, and in 1 of the 6 patients with atypical parathyroid adenoma (mean calcium of 13.5 ± 1.1 mg/dL; $p < 0.001$). The most frequent clinical signs in atypical adenoma patients were bone pain, fatigue, anorexia, abdominal symptoms (pain, dyspepsia, or reflux), and psychiatric symptoms. None of the patients had palpable masses in the physical examination, and all atypical adenomas appeared as single nodules. About 39.3% of the patients with parathyroid adenoma and 14.3 % of the patients with atypical parathyroid adenoma showed tumor recurrence after surgery (3).

The association between NF1 and hyperparathyroidism was described in few cases in the literature. Most of the reports describes parathyroid adenoma as the cause of hyperparathyroidism (16-19). We found one case report of the association between NF1 and parathyroid carcinoma (20).

Some authors believe that there is a genetic link between the two diseases due to the similarity of bone lesions common to them (20). In 1979, Chakrabarti suggested that the association between NF1 and hyperparathyroidism was another variation of multiple endocrine neoplasia, MEN 2B (16). In a 1997 study in Sweden, it was shown that neuroendocrine tumors (including parathyroid adenoma, pheochromocytoma, and thyroid gland C-cell hyperplasia) made up 25% of all tumors that occurred in NF1 patients (21).

More recently, two cases have been described in NF1 patients and C-cell hyperplasia with confirmed mutation of *NF1* and *RET* genes (6). *RET* proto-oncogene encodes a tyrosine-kinase receptor expressed in cells derived from the neural crest (22). Its mutation is responsible for MEN 2, whose incidence is estimated in 1: 35,000. This syndrome is divided into subtype 2A, in which thyroid medullary carcinoma, pheochromocytoma, and hyperparathyroidism are found; and subtype 2B, in which thyroid medullary carcinoma, pheochromocytoma, ganglioneuroma, and marfanoid habitus are found (23). Although many literature cases have described the association between NF1 and MEN 2, the reasons for this association are still unclear.

NF1 gene may have an essential role by means of its action on AMP-dependent protein kinase and Ras protein, activating signaling routes and, thus, controlling apoptosis and cell growth. It is supposed, based on these data, that *NF1* mutation may affect cell growth and differentiation of thyroid parafollicular C-cells and parathyroid cells (6).

Parathyroidectomy is a possible cure for primary hyperparathyroidism. A 50% reduction in intra-surgical PTH after 10 minutes of tumor resection may be used as a criterion for cure (2,4). In our case, PTH drop was 83% after 10 minutes of adenoma resection.

We reported here a rare association between NF1 and hyperparathyroidism due to an atypical parathyroid adenoma. In spite of the fact that tumor recurrence is more common in cases of adenocarcinoma, it may also occur in cases of atypical parathyroid adenoma (3). Therefore, the follow-up of these patients after surgery is important. As for NF1, despite lack of formal recommendation for laboratory screening of endocrine dysfunctions in patients that carry this disease (6,24), the possibility should be considered, and detailed analysis of clinical and familiar history may contribute for the diagnosis and early treatment of these diseases.

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