Possible Association between Carney Complex and Multiple Endocrine Neoplasia Type 1 Phenotypes

clinical case report

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ABSTRACT

Carney Complex (CNC) and Multiple Endocrine Neoplasia type 1 (MEN1) are forms of multiple endocrine neoplasia of dominant autosomal inheritance. Diagnosis of CNC occurs when two major criteria (lentiginoses, primary pigmented nodular adrenocortical disease, cardiac and cutaneous myxomas, acromegaly, testicular neoplasias, thyroid cancer) are observed and/or a major criterion associated with a supplementary criterion (affected relative, *PRKAR1A* gene mutation) occurs. On the other hand, diagnosis for MEN1 occurs through detection of two or more tumors located at the pituitary gland, parathyroid and/or pancreatic cells. The present case describes a 55 year-old male patient, diagnosed with acromegaly, primary hyperparathyroidism and papillary thyroid cancer, exhibiting components that meet the diagnostic criteria of both conditions described. Despite the occurrence of only one sporadic association or the acromegaly *per se* being responsible for the papillary cancer, new molecular mechanisms may not be ruled out. **(Arq Bras Endocrinol Metab 2008; 52/8:1356-1361)**

Keywords: Carney complex; Multiple endocrine neoplasia type 1; Acromegaly; primary hyperparathyroidism; Papillary thyroid cancer

RESUMO

Possível Associação entre os Fenotipos de Complexo de Carney e Neoplasia Endócrina Múltipla tipo 1.
Complexo de Carney (CNC) e neoplasia endócrina múltipla tipo 1 (MEN1) são formas de neoplasias endócrinas múltiplas de herança autossômica dominante. O diagnóstico do CNC ocorre quando dois critérios maiores (lentiginose, doença nodular pigmentosa primária das adrenais, mixomas cardíacos e cutâneos, acromegalia, neoplasia testicular, carcinoma de tireóide) são observados e/ou um critério maior associado a um critério suplementar (familiar afetado, mutação do gene *PRKAR1A*) ocorre. Por outro lado, o diagnóstico de MEN1 dá-se pela detecção de dois ou mais tumores localizados na glândula hipofisária, paratireóide e/ou células pancreáticas. O presente caso descreve um homem de 55 anos, com diagnóstico de acromegalia, hiperparatireoidismo primário e carcinoma papilífero de tireóide, exibindo critérios diagnósticos para as duas condições descritas. Embora possa ter ocorrido apenas uma associação esporádica, ou a acromegalia *per se* tenha predisposto ao carcinoma papilífero, novos mecanismos moleculares podem estar envolvidos. **(Arq Bras Endocrinol Metab 2008; 52/8:1356-1361)**

Descritores: Complexo de Carney; Neoplasia endócrina múltipla tipo 1; Acromegalia; Hiperparatireoidismo primário; Carcinoma papilífero de tireóide.

INTRODUCTION

CNC is an autosomal dominant multiple endocrine neoplasia syndrome (OMIM 160980) (1, 2). It is associated with skin and mucosal pigmen-

tation, cardiac and mucocutaneous myxomas, breast myxoma, primary pigmented nodular adrenocortical disease (PPNAD), prolactin and growth-hormone-producing adenoma, thyroid adenoma or carcinoma, psammomatous melanotic schwannoma, blue nevus, breast ductal adenoma, and osteochondromyxoma. Mutations of the protein kinase A regulatory subunit type 1A (*PRKAR1A*) gene have been implicated in the etiology of CNC. This gene encodes the type 1α regulatory subunit of protein kinase A (PKA), which is an important effector molecule in many endocrine signaling pathways (1).

MEN1 (OMIM 131100) is characterized by the occurrence of tumors in the parathyroid gland, in pancreatic islet cells and in the anterior pituitary (3). Besides the aforementioned major components, adrenocortical and carcinoid tumors, subcutaneous lipomas, facial angiofibromas and collagenomas have been associated with the disease (3, 4). MEN1 is a rare disease, with an estimated prevalence of 0.01 to 2.5 for 1000, representing 2-4% of all primary hyperparathyroidism cases (5). Most cases of MEN1 are inherited in an autosomal dominant pattern, but 8 to 14% of the affected patients might not have the familial form of the disease. Pituitary adenoma is an initial sign in 25% of the sporadic cases and in less than 10% in the inherited form of the disease. Inactivating mutations of the *MEN1* gene are associated with the development of endocrine tumors (6). To the best of our knowledge, the association between CNC and MEN1 has not yet been described in the literature. The present study aimed to describe a clinical case with the two phenotypes being associated.

SUBJECTS AND METHODS

Clinical case

A 55-year-old male patient with acromegaly diagnosed 6 years earlier was admitted to the hospital in 2005 for a follow-up. He was submitted to tumor resection through transsphenoidal surgery in 1998 and his case evolved to hypopituitarism (adrenal insufficiency, hypothyroidism and hypogonadism). He was using levothyroxine, corticosteroid and an anti-hypertensive drug. During the physical exams, patient presented clinical signs of acromegaly, multinodular goiter as well as skin papillomas and a thigh tumor suggestive of lipoma. Lentiginoses or any other signs of gastrointestinal tumor were not observed. In relation to family history, one of his nieces had a prolactinoma, but other endocrine neoplasias were not investigated.

The exams showed lack of suppression of the growth hormone (GH) after oral GTT (nadir 9.92ng/mL); increase in serum IGF-1 levels (622 ng/mL; reference range (rr): 78-258); hypercalcemia (total calcium 11.9mg/dL; rr: 8-10), hypercalciuria and elevated PTH intact (76.4 pg/mL; rr: 13-65), renal function, free T4 and prolactin at normal levels. Magnetic nuclear resonance (MR) showed macroadenoma (2cm) with supra- and parasellar extension (Figure 1). The skull x-ray showed a characteristic "salt-and-pepper pattern". Ultrasonography of the cervical region (USG) revealed three thyroid nodules (0.6-0.8 cm), one of them having microcalcifications. Fine needle aspiration punction suggested thyroid carcinoma. As serum calcium PTH intact levels continued to be higher, the patient was submitted to a total thyroidectomy and to a total parathyroidectomy with parathyroid auto-implantation at the same time. The anatomopathological study confirmed the papillary carcinoma (Figure 2) (encapsulated, not multicentric, measuring 1x0.7cm, with pathological staging T1NxMx) and the analysis of three parathyroid glands did not show alterations; the autoimplantated gland was not studied. Subsequently, the patient underwent a new surgery for resection of pituitary tumor and he received an ablative dose of iodine-131 after administration of recombining TSH, for complementation of the thyroid papillary carcinoma treatment. Testicular ultrasonography was normal and the echocardiogram did not show myxomas. Abdominal computed tomography revealed giant hepatic hemangioma, confirmed through scintillography with marked red blood cells. The patient had adrenal insufficiency confirmed by insulin tolerance test, so that the hypertension has been attributed to acromegaly. Thigh ultrasonography also suggested the lipoma. At present, patient shows normal calcium profile, in using octreotide and hormonal replacement for acromegaly and hypopituitarism control.

After obtaining the informed consent of the patient and the agreement of the Hospital Ethics Committee, mutational analysis of *MEN1* gene was performed. Genomic DNA was extracted from peripheral blood leukocyte (7), and twelve pairs of primers were used for polymerase chain reaction (PCR) amplifications of the nine coding exons of the *MEN1* gene and their corresponding 16 intron/exon boundaries. The PCR products were analyzed using a Genetic Analyzer 3100 Sequencer (Applied Biosystem, Foster City, CA, USA). However, no mutation of *MEN1* was detected in this patient.

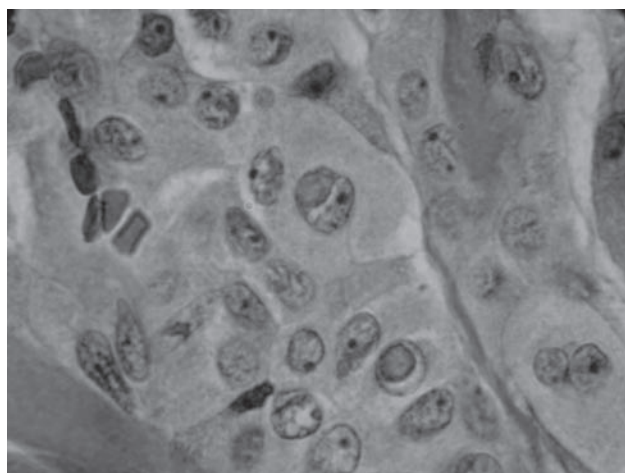**Figure.1.** Coronal T1 – weighted image demonstrates a large sellar mass with suprasellar extension.

Figure 2. Papillary thyroid carcinoma with intranuclear inclusions. H&E,x100.

In the examined family members of the patient (only his two daughters), both hypercalcemia and acromegaly signals were not seen and plasma levels of PTH intact, calcium, insulin, glucose, prolactin, GH and IGF1 were within the normal ranges. However, one of his daughters has alterations in hypophysis MR suggestive of a microadenoma, probably .a clinically non-functioning adenoma.

DISCUSSION

The present study describes the case of a patient affected by acromegaly that presented neoplastic components found in two types of multiple endocrine neoplasias, CNC and MEN1. These diseases, in spite of some shared clinical manifestations, including acromegaly and autosomal dominant inherited pattern, belong to different groups of endocrine neoplasias, with distinct molecular patterns whose association has not yet been described in the literature.

In relation to the first disease, diagnosis was established through the finding of two major criteria for CNC, specifically, acromegaly and differentiated thyroid cancer (Table 1), whereas the diagnosis of MEN 1 was established due to the presence of the GH-producing adenoma and primary hyperparathyroidism (3,4).

Table 1. Diagnostic criteria for CNC[a] (1).

Major criteria
1. Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa).
2. Myxoma (cutaneous and mucosal)[b].
3. Cardiac myxoma[b].
4. Breast myxomatosis[b] or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis.
5. PPNAD[b] or paradoxical positive response of urinary glucocorticosteroid to dexamethasone admistration during Liddle's test.
6. Acromegaly due to GH-producing adenoma[b].
7. LCCSCT or characteristic calcification on testicular ultrasonography.
8. Thyroid carcinoma[b] or multiple, hypoechoic nodules on thyroid ultrasonography, in young patient.
9. Psammomatous melanotic schwannoma[b].
10. Blue nevus, epithelioid nevus (multiple)[b].
11. Breast ductal adenoma (multiple)[b].
12. Osteochondromyxoma[b].
Supplemental criteria
1. Affected first-degree relative.
2. Inactivating mutation of the PRKAR1A gene.

[a] To make a diagnosis of CNC, a patient must either: 1) exhibit two of the manifestations of the disease listed, or 2) exhibit one of these manifestations and meet one of the supplemental criteria (an affected first-degree relative or an inactivating mutation of the PRKAR1A gene); [b] With histological confirmation.

Mutations of the gene *PRKAR1A,* a tumor suppressor located in the 17q24 chromosome, have been implicated in the etiology of CNC in almost 50% of the affected patients (1, 8). Loss of PKA regulatory subunits increases its catalytic activity, providing cellular proliferation in various tissues, which results in endocrine hyperfunction and the development of neoplasias. They are germ mutations, in heterozygosis, resulting from an unexpressed allele, which leads to haploinsufficiency (2). On the other hand, in MEN1 the causative gene, located in the 11q13 chromosome, consists of 10 exons and encodes a protein, composed of 610 amino acids, called menin (3, 5). Even though the functional role of this protein has not yet been totally elucidated, inactivating mutations in this gene are associated with the development of endocrine tumors (6).

The inactivation of this gene follows the Knudson model, and consequently the phenotypic expression of germ mutation is only evidenced after somatic deletion of the second allele, called loss of heterozygosity (LOH) (9-12). In the CNC, LOH as a model of gene inactivation is a rare event, as shown in the genetic analysis of tumors in affected patients (9).

Several studies indicate that patients presenting isolated acromegaly present a higher risk of developing malignant and benign tumors (13-17), due to the increased levels of GH and IGF-1 (17,18). A 5.6% prevalence of differentiated thyroid carcinoma was observed in acromegaly patients, significantly higher than in the general population (0.093%) (19,20). Calculated risk of thyroid carcinoma in these patients appears to be 60 times higher than that in the general population. Prevalence of these carcinomas in MEN1 has been reported in some studies as incidental, due to the fact that thyroid neoplasias are more frequent than MEN1 (21).

In CNC the incidence of thyroid cancer has been estimated as 1.4% (1,2). In a previous study, a transgenic mouse carrying an antisense transgene for *PRKAR1A* developed thyroid follicular hyperplasia and adenomas (22), supporting the role of this gene in thyroid tumorigenesis. But histologically, thyroid cancer associated with CNC differs from sporadic cases by being multicentric and more aggressive (23), characteristics that were not observed in the patient described above.

In relation to the GH tumor secretor, in most CNC patients, somatic cell hyperplasia anticipates the formation of GH secretor adenoma, but in MEN1, this event was not observed in acromegaly patients (24).

In MEN1, hyperparathyroidism is present in 90 to 97% of the patients, generally as a primary manifestation, as the consequence of two or more parathyroid hyperplasias, contrary to sporadic cases that have only one parathyroid adenoma as the most frequent cause (4,5). In CNC no occurrence of compromised parathyroid was found. In general, osseous alterations found in CNC patients are a consequence of associated hypercortisolism. Thus, because PTH signaling also depends on PKA activation, the osseous metabolism alterations found in CNC patients can also be related to the excessive action of this hormone (2). In this case report the patient presented increased calcium and PTH intact after surgery, but these parameters subsequently normalized. Therefore, it is possible that the auto-implanted parathyroid was hyperplastic.

Hemangiomas constitute the majority of benign hepatic neoplasms and are nine times more frequent in females than in males. Most cases are sporadic; however, they are occasionally inherited in autosomal dominant fashion with moderate to high rates of penetrance (25). Hemangioma has not been reported as being associated with either MEN1 or CNC to the best of our knowledge. There is a case report on HPP, thyroid cancer and capillary hemangioma of the left external auditory meatus, but no mutations of *MEN1* or *RET* genes were detected (26).

Our finding of no *MEN1* gene mutation in this patient may be related to the presence of disease phenocopy, to large deletions that are missed by DNA sequencing (27), to intronic mutations not detected by current primers or to mutations in regulatory elements or untranslated exons of the *MEN1* gene, that were not tested in the present and earlier studies (28,29). Unfortunately, anomalies of *PRKAR1A* in the present patient cannot be examined but will be the next step.

Another possibility for this case is an occurrence of the clinical condition termed FIPA (familial isolated pituitary adenomas) that refers to relatives with two or more pituitary adenomas that are genetically negative for mutations in *MEN1* or *PRKAR1A* (30). All pituitary tumor phenotypes are reported in heterogeneous FIPA, however, almost invariably at least one prolactinoma or GH-secreting adenoma is seen per family. A recent whole-genome DNA mapping study identified inactivating mutations in the gene that encodes aryl hydrocarbon receptor interacting protein (*AIP*) gene on chromosome 11q13.3 (31).

In the reported case sporadic association of genetic alterations found in MEN1 and CNC might have occurred. On the other hand, acromegaly *per se* could have facilitated the development of thyroid cancer, since there is a high incidence of thyroid cancer in patients that present excess of GH and IGF-1 (18). However, it is impossible to rule out that new molecular mechanisms, located in different chromosomal regions, distinct from the ones described until now, may have been the cause of different neoplasias described in the patient. The molecular biology approaches are expected to reveal mechanisms of endocrine tumorigenesis in order to develop better diagnostic, prognostic and therapeutic tools.

No potencial conflict of interest relevant to this article was reported.

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