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Case Study

Multiple Endocrine Neoplasia 2a: Case Report and Review of Literature

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Abstract

Multiple endocrine neoplasia is a hereditary, autosomal dominant disease. It is created predominantly by RET germline mutations and is considered rare, with a frequency of 1 in 30,000 people. In particular, medullary thyroid cancer associated to this pathology presents at a younger age in relation to sporadic cases. Pheochromocytoma is linked to metastatic disease in only 4% of cases and it is a disease which requires high clinical suspicion. The age of presentation when related to multiple endocrine neoplasia is lower than that of the general population, 38 and 47 years of age respectively. RET proto-oncogene mutation on Codon 634 in exon 11 is the most frequent genetic alteration, present in 85% of cases of MEN2A. Its penetrance for pheochromocytoma is 25% at 30 years and 88% at 77. The objective of this article is to present a case of a patient with MEN2A with bilateral pheochromocytoma and medullary thyroid cancer, discovered in a hypertensive man as an incidental finding.

Introduction

Multiple endocrine neoplasia is divided into three main syndromes, type 1, type 2A, familial medullary thyroid cancer and type 2B. Type 2A is characterized by the presence of medullary thyroid cancer in 95% of cases, pheochromocytoma in 50% and parathyroid hyperplasia in 20–30%. The presence of two or more are necessary to define the disease. The most frequent genetic abnormality in this disease are germinal mutations in the RET gene, located in chromosome 10q11.2. It has an autosomal dominant hereditary pattern and a prevalence of 1.3 in 100,000 individuals (Figure 1). The most common mutations are present in exon 10, particularly in codons 609, 618 y 620 and exon 11 in codon 634. The latter represents 85% of cases and a higher association with hyperparathyroidism and pheochromocytoma [1].

It has been documented that according to the mutation in the RET gene and its association to pheochromocytoma, particularly codon 634 and so, genotype C634R are related to metastatic disease.

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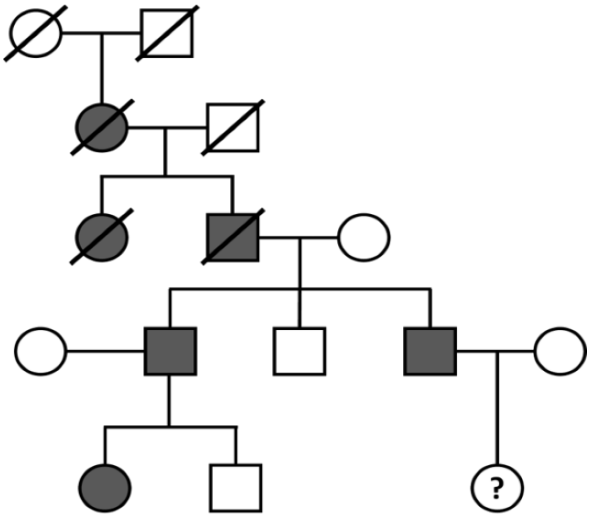

Figure 1: Family tree, with classic autosomal dominant inheritance.

The presence of haplotypes with three or more polymorphic alleles are also linked to metastatic disease [2,3]. According to the mutated codon, recommendations exist for different age groups in relation to performing thyroidectomy. For codon 634 mutations it must be done at 5 years of age and screening for pheochromocytoma, and hyperparathyroidism should begin at age 8 [1,4]. The most common RET mutation in MEN2A Spanish patients is Cys634tyr (C634Y) and 634R in European countries (except Italy where Va1804Met is more common [5]. The molecular evidence contemplates p.Cys618. Arg mutation as an ancestral mutation that has spread in Cyprus due to a possible founder effect [6,7].

Objective

To present a case of a patient with type 2A multiple endocrine neoplasia with bilateral pheochromocytoma and a stage II medullary thyroid cancer.

Case presentation

This is the case of a 53-year-old man, diagnosed at 43 with arterial hypertension, treated with amlodipine, valsartan hydrochlorothiazide and metoprolol, with occasional uncontrolled hypertension up to 190/100mm/hg. The patient was also in follow up for prostatic hyperplasia, with ultrasounds conducted up to once a year. An incidental tumor was found by ultrasound in the right adrenal gland, so a contrasted, abdominal CT scan was conducted to evaluate the lesion. The scan showed hyper vascular solid lesions in the arterial phase in both adrenal glands, suggestive of a paraganglionic origin of a possible bilateral pheochromocytoma. The lesion on the right gland measured 45x37x43mm with 37HU and an absolute washout of 44.2%, while the lesion on the lest measured 45x28x46mm with 50HU and an absolute washout of 88.6%. Evaluation was conducted specifically for pheochromocytoma, with elevated free and total metanephrines as well as normetanephrine. A bilateral adrenalectomy was performed. Because of the suspicion of a multiple endocrine neoplasia, a PET with imaging tracers for the dopaminergic system were conducted, documenting tumoral lesions on the thyroid gland suggestive of neoplasia. A neck ultrasound was performed, which reported two nodules in the right thyroid gland

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classified as TI-RADS 4 and three nodules in the left thyroid gland, classified as TI-RADS 5. A total thyroidectomy is performed with a central lymph node dissection with a pathological diagnosis of stage II medullary thyroid cancer. Afterwards, genomic findings showed an alteration in RET, specifically a Cys634Tyr exon 11 mutation.

Discussion

In the aforementioned clinical case, patient with drug resistant arterial hypertension is presented, which is defined as the persistence of uncontrolled blood pressure with the use of the maximum dose of three antihypertensive medications, one of which must be a thiazide diuretic [8]. The patient was asymptomatic though in this context, it is important to look for causes of secondary hypertension. Particularly in this case, imaging studies were conducted for other reasons, finding an adrenal lesion which gave way to a diagnostic approach tailored towards identifying pheochromocytoma. This diagnosis consists of the evaluation of catecholamines and their metabolites in serum or in a 24-hour urine sample, with an elevation 3 times the upper limit of normal. According to studies by Pecak et al., a diagnosis of pheochromocytoma may be discarded when the neurotransmitter production is exclusive to norepinephrine [9].

In this case, the diagnosis was made when the patient was 53, with a previous history of hypertension since age 43. According to the age of diagnosis for patients with a diagnosis of MEN2A [7], pertaining to pheochromocytoma, it is associated with a younger age at diagnosis, specifically 38 vs 47 years. The form of presentation is also different to the general population, as it is more frequent for patients with MEN2A to have asymptomatic pheochromocytomas (52 vs 0%). Bilateral disease has also been evaluated and found in 83% of cases related to multiple endocrine neoplasia, such as the featured case. Relating specifically to the genomic studies, it is recommended to conduct them with tumors associated to MEN are found at 17-24% of pheochromocytomas even though sporadic in origin, have a hereditary basis, with a mutation in RET in 5% of cases. The probability of a pheochromocytoma being hereditary can be as high as 84% if multifocal or bilateral, such as the case is presented, 56% if diagnosed before age 18. This may be done by genome sequencing or specific exome sequencing, showing a high sensibility and a specificity of 98% for MEN2A [1]. In the case of current patient, sequencing was conducted for RET, in particular, exon 1. A Cys634Tyr (C634Y) mutation was detected, which has a penetrance of 25% at 30 years of age, 52% at 50 years of age and 88% at 77 [2]. There could be clinical differences caused by different amino acid substitutions at codon 634, the C634R mutation was associated with a more aggressive MEN 2A phenotype than the C634Y mutation [5]. Others report Pheochromocytoma as a first manifestation MEN2A with RET mutation S891 A [10]. Treatment will be administered differently depending on each neoplasia. For localized or locally advanced medullary thyroid cancer, the standard of treatment is a total thyroidectomy with a cervical lymph node dissection, which may be tailored to findings in a preoperatory ultrasound of calcitonin levels. An absence of lymph nodes in the neck ultrasound still merits a thyroidectomy and a central lymph node dissection. The extent of lymph node dissections will also be determined by levels of calcitonin [11]. If there is a positive imaging study regarding lymph nodes, a central and ipsilateral lymph node

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dissection of the neck is warranted and must also be taken into consideration if calcitonin is above >200pg/ml.

Patients with calcitonin levels <10pg/ml after surgery with a complete lymph node dissection may be considered cured, with 10year survival rates close to 98% [11]. Regarding systemic treatment, there have been multiple small phase II trials conducted which evaluate the effectiveness of different chemotherapy regimens with discrete responses [12], which is where targeted therapy gains its importance. Firstly, vandetanib vs. placebo is studies, finding statistically significant differences in progression free survival and response rates [13-15]. Similar results have been observed with cabozantinib [16]. Another recently investigated drug is selpercatinib, inhibiting RET directly and offering higher response rates [17]. Pertaining specifically to the management of pheochromocytoma, the standard of care is surgery. Studies have compared unilateral, bilateral and adrenal cortex conserving surgeries, without finding differences in recurrence of pheochromocytoma with the different proposed surgeries, but greater steroid dependency regarding more radical surgeries [18].

Conclusion

An interesting and rare case report on Multiple Endocrine Neoplasia 2a has been represented. After the evaluation of the patient, first degree family members needed to be also evaluated, finding the same mutation. Medullary thyroid cancer and pheochromocytoma are unusual, infrequent neoplasia, and their association with multiple endocrine neoplasia must be properly identified, as 24% of sporadic pheochromocytomas have a hereditary origin. In this context, genetic counseling is especially relevant because of the impact it can have on the patient and their family.

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