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Multiple Endocrine Neoplasia Type 2A: Case Report

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Rezumat

Sindrom de neoplazie endocrină multiplă tip 2A: prezentare de caz

Sindromul de neoplazie endocrină multiplă tip 2A (MEN 2A) reprezintă un sindrom genetic cu transmitere autozomal dominantă caracterizat prin asocierea carcinomului medular tiroidian, feocromocitomului şi hiperparatiroidismului primar. Identificarea mutațiilor germinative ale genei RET (REarranged in Transfection) la pacienții cu unul sau două dintre componentele sindromului sau prezența tumorilor specifice la rude permite stabilirea diagnosticului. Prezentăm cazul unei familii cu sindrom MEN 2A la care analiza genetică a confirmat mutația genei RET la nivelul codonului 634, prezentă la tată (DV) în vârstă de 48 de ani şi la fiică (DM), în vârstă de 20 de ani, ca particularitate fiind descoperirea cazului index în descendență (la fiică, la care boala a debutat prin feocromocitom), ulterior, prin screening hormonal, imagistic şi genetic fiind depistat şi tatăl. Această familie susține fenomenul de anticipație descris în cadrul sindroamelor MEN prin care, în generații, boala se manifestă mai devreme şi are trăsături mai severe.

Cuvinte cheie: sindrom MEN 2A, mutații RET, screening genetic

Abstract

Multiple endocrine neoplasia type 2A (MEN 2A) is a complex autosomal dominant inherited syndrome characterized by medullary thyroid carcinoma (MTC), pheochromocytoma and primary parathyroid hyperplasia. In patients with only one or two clinical features, identification of a germline RET (REarranged in Transfection) mutation or the identification of the clinical features of MEN 2A in other first degree relatives is required to make the diagnosis. We present the case of a family with MEN 2A syndrome confirmed by genetic analysis which identified RET gene mutation in 634 codon in father - DV - aged 48 years and also in daughter DM - aged 20 years. The specific feature in this case is that the index case was the daughter (diagnosed and operated for pheochromocytoma at the age of 19 years), the father being diagnosed later with medullary thyroid carcinoma by mutational screening in all family members. This family supports the phenomenon of anticipation, in which severity increases and the age of onset decreases in successive generations, the syndrome being discovered earlier and with a worse prognostic in the daughter.

Key words: MEN 2A, RET mutations, genetic screening

Introduction

Multiple endocrine neoplasia type 2 (MEN 2) is an autosomal dominant syndrome characterized by occurrence of distinct proliferative disorders of endocrine tissues. MEN 2 is characterized by medullary thyroid carcinoma, pheochromo-

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cytoma and primary parathyroid hyperplasia and is subclassified into three distinct syndromes: MEN 2A, MEN 2B and familial medullary thyroid carcinoma. MEN 2 is caused by germline activation of an oncogene, RET (Rearranged in Transfection) (1) that encodes a receptor tyrosine kinase which is required for the normal growth and maturation of cells derived from the neural crest (2,3). Mutational analysis of the RET gene has been used in the diagnosis and management of patients with MEN 2 variants (4).

Early diagnosis by screening of family members in MEN 2 kindred is essential because medullary thyroid cancer is a life-threatening disease that can be cured or prevented by early thyroidectomy (5). Patients with medullary thyroid cancer can be cured only by complete resection of the thyroid tumor and any local or regional metastases (6). Because of the very high frecquency of multicentric lesions total thyroidectomy is recommended (7). A comprehensive prophylactic central node dissection is recommended for all patients with palpable primary tumors or recurrent disease.

Pheochromocytoma occurs in approximately 40% of patients with MEN 2A (8). Bilateral adrenalectomy should usually be limited to patients with bilateral pheochromocytomas and in patient with unilateral disease in whom other family members have had unusually aggressive bilateral adrenal medulla disease. Unilateral adrenalectomy in those patients who have a normally appearing controlateral gland is more appropriate (9).

Case report

DM patient, aged 19 years, was admitted to the internal medicine clinic for hypertensive crisis followed by orthostatic hypotension, with suspicion of a pheochromocytoma. Abdominal CT scan confirmed the presence of a right adrenal tumor of 6 cm, operated by right classic adrenalectomy; histopathological examination confirmed the diagnosis of pheochromocytoma (Fig. 1).

Given the young age of disease onset and pathological confirmation of the diagnosis of a chromaffin tumor, in conjunction with family history (two paternal relatives who died at 16 and 17 years), the suspicion of MEN 2A syndrome was raised and the genetic testing to identify RET gene mutations were performed.

Until genetic screening results were obtained, we initiated biochemical, hormonal and imaging testing of all family members and the father proved to present a thyroid nodule of 1.42/1.17/2.86 cm with irregular borders, hypoechoic structure (Fig. 2) and also calcitonin values of 441 pg/ml (normal value from 1 to 11.8 pg/ml). Fine needle biopsy confirmed adenomatous nodule with carcinomatous degeneration of medullary thyroid carcinoma type. Normetanephrine and metanephrine values in plasma and urine were normal and no adrenal tumor was detected by CT screening. The father was submitted for total thyroidectomy with radical neck lymph node dissection; histopathological examination confirmed medullary thyroid carcinoma (Fig. 3 A, B).

Simultaneously, the RET gene analysis confirmed mutation

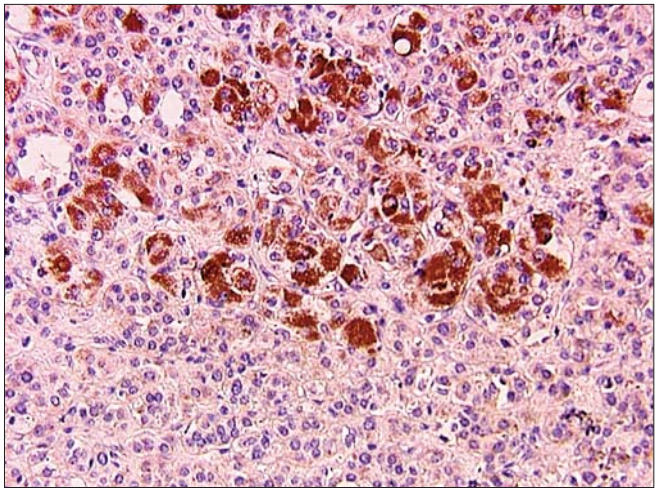


Figure 1. *Histopathological aspect of chromaffin tumor*



Figure 2. *Thyroid ultrasound: thyroid nodule of 1.42/1.17/2.86 cm with irregular borders, hypoechoic structure*

at codon 634 (c.1902C>G, p.C634W leading to substitution of cysteine with tryptophan in RET receptor structure) for the daughter and the father, but not for the brother and the mother. Genotyping for codon 634 sequence changes in RET gene using high-resolution melting (HRM) analysis revealed 2 different melting curves for the family members analysed, one of these similar to that of the heterozygous control – identified in the index case and her father (Fig. 4). Sequencing of Polymerase Chain Reaction (PCR) products of the exon 11 of RET gene identified a germline heterozygous mutation (c.1902C>G, p.C634W) in 2 of the family members, the other 2 being wild-type, thus confirming the HRM results (Fig. 5).

The daughter, aged 20, was further investigated by screening for medullary thyroid carcinoma. Thyroid ultrasound revealed a transsonic septated right lobe thyroid nodule and two left lobe nodules and the biochemical evaluation showed elevated calcitonin (44,40 pg/ml) and chromogranin (124 pg/ml) levels, elements that recommended thyroid surgery. Normetanephrine and metanephrine values both in plasma and urine were normal after surgery for pheochromocytoma and adrenal CT scan showed no left adrenal tumor. Hormonal

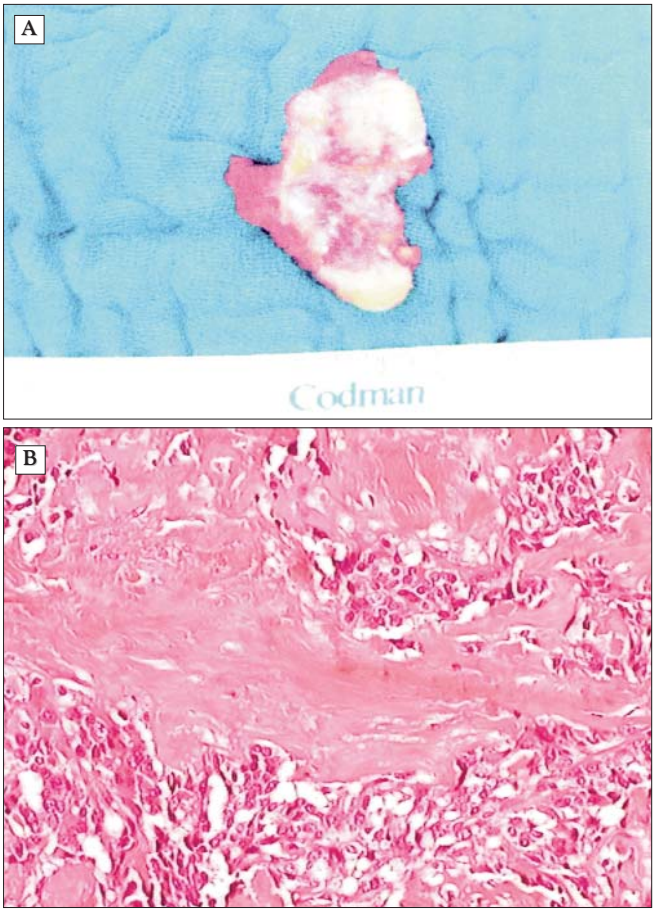


Figure 3. *(**A**) Macroscopic aspect of medullary thyroid carcinoma; (**B**) Histopathological aspect of medullary thyroid carcinoma*

screening in both carriers of the genetic defect was negative for primary hyperparathyroidism.

Discussion

It is unusual for pheochromocytoma to precede the development of MTC and be initial manifestation of MEN 2, like in our case. In patients who have undergone regular screening, pheochromocytomas have usually become evident about 10 years later than C cell hyperplasia or MTC (10). Thus, pheochromocytomas in MEN 2 are identified during screening or through heightened vigilance for symptoms (paroxysm of anxiety, headache, diaphoresis, palpitations or tachycardia) in patients with known or suspected MEN 2. Rarely pheochromocytoma may be the first manifestations of MEN 2 (11).

In a MEN 2A family, a sample from one subject already known to be affected should be tested in order to determine the specific RET mutation for that family, like we did in our case. All subjects of unknown status in that family should then be definitively genotyped for detecting RET mutations carriers. Genetic screening in our case showed the same mutation of the RET gene to father who had presented at the time of diagnosis medullary thyroid carcinoma.

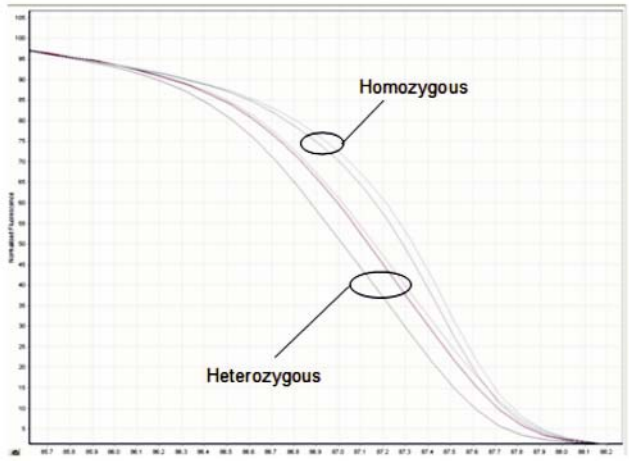


Figure 4. *High-resolution melting (HRM) analysis of the amplicon of RET gene containing codon 634: 2 melting curves allowing the identification of heterozygous curves*

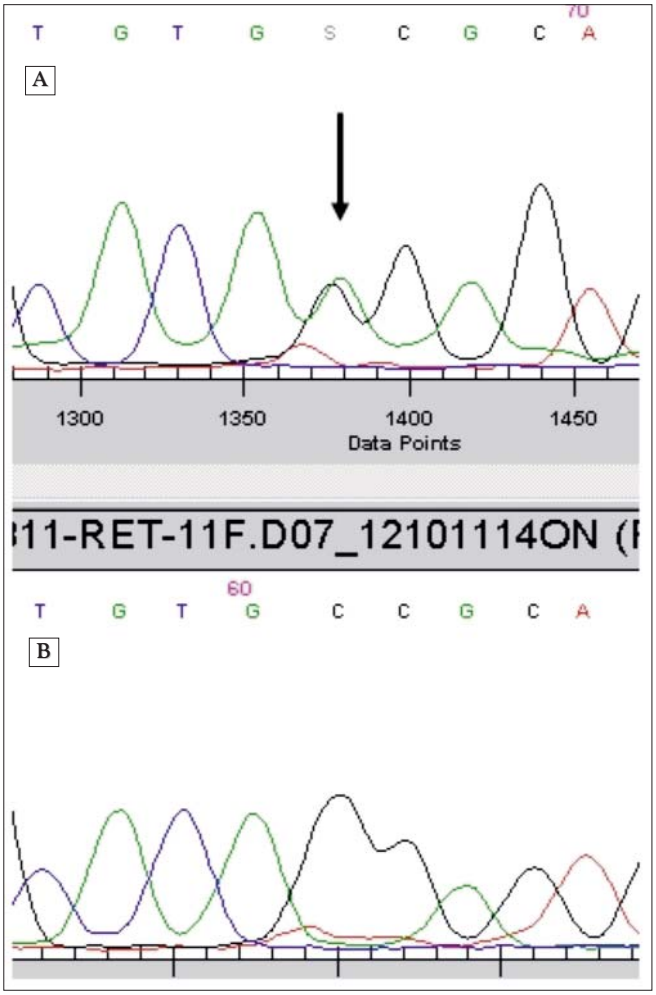


Figure 5. *RET exon 11 chromatogram of the index case: heterozygous change C\G in nucleotide 1902 of RET gene (c.1902C>G, p.C634W - arrow, panel **(A)** compared to wildtype sequence chromatogram (panel B)*

Conclusions

The particularity of this family with MEN 2A syndrome is the discovery of index case in daughter, aged 20 years old, diagnosed first with unilateral pheochromocytoma. Only by subsequent hormonal screening and imaging the father was diagnosed with medullary thyroid carcinoma; the genetic screening confirmed the presence of the familial syndrome.

The disease onset by pheochromocytoma (with penetrance of only 40-50% in MEN syndrome) at a young age and with subtle symptoms and the discovery of the index case in a family with MEN 2A syndrome initially in the child and only later on ascending line to the father, is a less common diagnostic method.

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