Multiple endocrine neoplasia type 2a and germ line C634G RET mutation diagnosed in an 80-year-old patient

Néoplasie endocrinienne multiple de type 2a et mutation C634G du proto-oncogène RET diagnostiquées chez un patient de 80 ans

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Abstract

An 80-year-old man presented with progressive fatigue. Blood tests showed that serum calcium was increased (2.93 mmol/l, normal range 2.20–2.55 mmol/l) and serum concentration of intact parathyroid hormone (iPTH) inappropriately high (198 pg/ml, normal range 15-85 pg/ml). Neck ultrasonography and Tc-MIBI scintigraphy revealed a right parathyroid adenoma and a multinodular goiter. Serum calcitonin was significantly increased (220 pg/ml, normal range < 10 pg/ml). Concomitantly, a chest-abdominal computed tomography was performed and revealed a 22 mm right adrenal incidentaloma. The urinary catecholamines and metabolites were two-fold above the upper limit of normal. After right adrenalectomy which confirmed the diagnosis of pheochromocytoma, the patient underwent total thyroidectomy with dissection of the central lymph node compartment and right parathyroidectomy. On histopathologic examination, both thyroid lobes presented 13 foci of MTC without lymph node metastasis and the parathyroid gland presented a benign adenoma without hyperplasia. The patient underwent screening and genetic testing revealing a germ line C634 G RET mutation. The diagnosis of Men2a at the age of 80 years and the absence of lymph node metastasis of the multiple MTC in a carrier of C634G mutation were unusual and argued for the possible role of genetic modifier(s) in this MEN 2a patient.

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1. Introduction

Activating mutations of the Rearranged during transfection (\textit{RET}) proto-oncogene mapped to chromosome 10q11.2 are associated with clinical syndromes such as familial medullary thyroid carcinoma (MTC), multiple endocrine neoplasia type 2a (MEN 2a with MTC, pheochromocytoma, parathyroid adenoma) and multiple endocrine neoplasia type 2b (MEN 2b with MTC, pheochromocytoma, intestinal ganglioneuromatosis, marfanoid habitus). These inherited cancer syndromes are transmitted as an autosomal dominant trait with a high degree of penetrance and variable clinical expression. Recent studies have demonstrated the existence of an age-related progression from C cell hyperplasia (CCH) MTC and, ultimately, presence of nodal metastasis [1]. Consequently, the timing and the extent of surgical resection may be guided by the genotype-phenotype correlations [1]. In patients with \textit{RET} mutations in codon 634, MTC appears commonly before the age of ten, and the interval from tumor development to nodal metastasis is less than ten years. Therefore, patients with germ line \textit{RET} mutations at codon 634 should have total thyroidectomy with central lymph node dissection prior to 5 years of age [2,3].

We report an exceptional case of MEN 2a with multifocal MTC without lymph node metastasis, pheochromocytoma and hyperparathyroidism diagnosed in an 80-year-old man with germ line C634G (c.1900T \textgreater G) \textit{RET} mutation.

2. Case report

An 80-year-old male patient consulted for progressive fatigue. His past medical history was marked by a euthyroid multinodular goiter, chronic respiratory insufficiency and prostate cancer surgically treated 15 years ago. On biochemical evaluation, serum calcium was increased (2.93 mmol/l, normal range 2.20–2.55 mmol/l) with high urinary calcium excretion (481 mg per day) and an inappropriately high serum concentration of intact parathyroid hormone (iPTH) at 198 pg/ml (Elecsys, normal range 15–85 pg/ml). A dual energy X-ray absorptiometry (DEXA) was performed and the bone mineral density was equal to 3.5 standard deviations below that of a young adult reference population (T-score). Neck ultrasonography and Te-MIBI scintigraphy revealed a right parathyroid adenoma. Concomitantly, in view of the respiratory insufficiency, a chest-abdominal computed tomography was performed and revealed a 22-mm right adrenal incidentaloma and two vertebral fractures. On clinical examination, blood pressure was 160/105 mmHg and the patient had no clinical evidence of Cushing’s syndrome. The urinary catecholamines and their metabolites were two-fold above the upper limit of normal range (epinephrine 53 \mu g per 24 hours, normal range <20 \mu g per day; metanephrine 772 \mu g per 24 hours, normal range <350 \mu g per day). After a preoperative treatment with alpha receptor blocker and volume expansion, laparoscopic exploration confirmed a right adrenal tumor. On histopathologic examination, the adrenal mass was a pheochromocytoma without sign of malignancy.

At the same time, neck ultrasonography confirmed a multinodular goiter. The two largest (12 mm) nodules were located in the right thyroid lobe. Serum TSH level was normal (2.5 \mu U/ml, normal range 0.3–4.0 \mu U/ml). Serum calcitonin level was significantly increased (220 pg/ml, normal range <10 pg/ml). After right adrenalectomy, the patient underwent a total thyroidectomy with systematic dissection of the central lymph node compartment (17 lymph nodes were removed) and identification of the four parathyroid glands followed by a right parathyroidectomy. On histopathologic examination, both thyroid lobes presented 13 foci of medullary thyroid carcinoma without peritumoral CCH. No lymph node metastasis was found, blood vessels were not invaded, and the thyroid capsule was intact. Finally, the parathyroid gland presented a benign adenoma without hyperplasia. After surgical treatment, serum calcium level and serum concentration of iPTH were in the normal range, basal calcitonin level was less than 2 pg/ml and urinary catecholamines and metabolites levels were normalized. High blood pressure was still uncontrolled and antihypertensive treatment was needed.

After written informed consent and in accordance with institutional guidelines, the patient underwent screening and genetic testing for the identification of germ line \textit{RET} mutations. The patient had germ line C634G (c.1900T \textgreater G) \textit{RET} mutation but genetic analysis did not reveal G691S and A432A \textit{RET} polymorphism respectively associated with a younger age at diagnosis [4] and MTC without MEN 2a syndrome components [5]. However, the biological significance of these \textit{RET} polymorphisms remains unclear. Since he had no children and no siblings, no familial genetic screening was performed.

3. Discussion

In humans, germline mutations of \textit{RET}, encoding a membrane tyrosine kinase receptor (TKR), affect the development and/or proliferation of four types of tissues deriving from neural crest cells: thyroid C cells, parathyroid cells, chromaffin cells of the adrenal medulla and enteric autonomic plexus. Mutations affecting the extracellular domain (codons 609, 611, 618, 620, 630, and 634) activate the TKR by ligand-independent dimerization and cross-phosphorylation. Intracellular domain mutations affecting codons 768, 790, 791, 804, and 891 of \textit{RET} may interfere with intracellular ATP binding. Moreover, the mechanisms of \textit{RET} activation might determine the pace of malignant transformation from C cell hyperplasia to MTC. Among patients with node negative MTC, those with intracellular-domains mutations were younger than those with extracellular-domains mutations [6–8].

On the other hand, the multicenter European multiple endocrine neoplasia (EUROMEN) study [1], investigating the pace of early malignant progression to hereditary thyroid carcinoma among asymptomatic carriers of \textit{RET} mutations, reported a significant aged-related progression from C-cell hyperplasia to MTC and, ultimately, presence of nodal metastasis according to affected codons. In asymptomatic carriers of \textit{RET} germ-line mutations in codon 634, malignant progression from C cell hyperplasia to MTC may occur during the first years of life. Once malignant transformation has taken place, lymph node metastasis occurs on average 6.6 years later. Therefore, accord-
ing to the Euromen study, cumulative risk of MTC among the carriers of RET mutations at codon 634 was 1 at 20 years.

Thus, age at diagnosis and aggressiveness of MTC differ between the RET germ line mutations [9]. RET mutations in codon 634 predispose to younger age of diagnosis [10]. However, Puñales and co-workers reported the case of three Brazilian women with an asymptomatic MTC (62, 65 and 73 years old) in a family harboring a C634Y mutation. The 65-year-old patient underwent surgery and the histopathologic examination revealed a 2 cm nodule on each lobe with MTC and CCH. The other patients refused the surgery but guided-fine needle aspiration confirmed MTC. The three women had no pheochromocytoma or primary hyperparathyroidism [11].

Lymph node metastases are significantly more frequent in patients with multifocal than unifocal MTC [12]. Our 80-year-old patient had numerous foci of MTC without lymph node metastasis and genetic screening revealed a germline C634G RET mutation.

To our best knowledge, our patient is the oldest index case so far reported with 634 RET mutation and is also remarkable by the absence of lymph node metastasis despite multifocal MTC.

The clinical presentation of MEN 2a varies among families with different mutations but also within families where patients carry the same mutations [1,8]. In most studies, age at diagnosis did not seem to differ significantly among the various nucleotide and amino acid exchanges for a specific codon. However, Puñales and co-workers [11] suggested that specific nucleotide and amino acid exchange in RET codon 634 had a direct impact on tumor aggressiveness. They studied 17 Brazilian families with germ line RET mutations, and they observed that individuals with the C634R, the most frequent genotype, had significantly more distant metastasis than those with the C634Y or C634W mutations, despite similar age at diagnosis. The limited number of patients and families (only ten patients and four families with C634R mutation) restricts their conclusions. Moreover, they took no account for statistical limitation due to multiple testing and the influence of other hereditary molecular events could not be excluded. Unfortunately, no studied patient had the C634G RET mutation found in the reported patient, but other data have suggested that this rare mutation is associated with an early malignant transformation of thyroid C cells and a high risk of nodal metastasis from MTC [1].

The intrafamilial phenotypic variations regarding the clinical signs and the age at diagnosis suggest a role for genetic modifiers, which may work through quantitative effect [6]. RET transgenic mouse model also suggests the presence of modifier gene(s) [13]. In a human study including symptomatic patients operated on for MTC [9], RET genotypes were correlated with age at diagnosis (634 codon predisposed to younger age at diagnosis), but no correlations were encountered between RET mutations and the scoring systems (TNM, UICC).

Recently, it has been reported that single nucleotide polymorphism(s) (SNP) within RET gene may increase susceptibility to MTC and may have such modifier effect on the age of onset or the aggressiveness of MCT. Robledo and co-workers [4] analyzed the G691S (exon 11) and S904S (exon 15) RET polymorphisms in 198 individuals corresponding to 35 unrelated MEN 2a families. They found that the homozygous patients for these polymorphisms were, on average, 10 years younger at diagnosis compared with heterozygous and wild-type patients suggesting that the G691S and S904S variants of RET have a modifier effect on the age of onset of MEN 2a. However, Lesueur and co-workers could not confirm this association in a large cohort of 384 individuals from MEN 2a families from four different European populations [14]. They found a weak positive association between A432A RET polymorphism and phenotypic expression. The rare allele for this variant was overrepresented in patients carrying a mutation at codon 634 and who developed MTC alone compared with patients who developed MTC and other MEN 2a syndrome components [14]. These studies [4,14] gave no precise mechanism(s) by which these polymorphisms of RET may affect the age of the onset of MTC in patients with MEN 2a. In a more recent study [5], six low penetrance genes related to RET signaling pathway/functions or involved in tumorigenesis (BCL2, STAT1, HRAS, CDKN2B, CDK6, COMT and AURKA) were associated with the risk of sporadic MTC. Their potential modifier role for hereditary MTC development remains to be studied. Further studies using large scale genotyping methods in combination with case-control study are necessary for better understanding of the molecular mechanism(s) of clinical heterogeneity in patients with MEN 2a.

In conclusion, to our best knowledge we report the oldest patient with MEN 2a due to a C634G RET mutation. Both the age at diagnosis (80 years old) and the absence of lymph node metastasis of multifocal MTC in this patient attested an unusual clinical phenotype with later age of onset and reduced tumor aggressiveness, and suggest the possible role of genetic modifier(s). But, we have to keep in mind that according to the current recommendations, patients with any RET codon 634 mutation must be classified as having a high risk for MTC.

References


