A Family Diagnosed as MEN2A with a Rare Mutation D631Y in RET Oncogene

O Aldemir[1], M Ozsan[2], H Gökce[3], I Ustun[2], S Okuyucu[4], D Berker[5], S Güler[5], C Gökçe[2]

ABSTRACT

Multiple Endocrine Neoplasia type 2A (MEN 2A) is an autosomal dominant disease including medullary thyroid carcinoma (MTC), pheochromocytoma and primary hyperparathyroidism. Germline mutations in the RET proto-oncogene are well documented as the genetic cause of multiple endocrine neoplasia type 2A (MEN2A) and familial medullary thyroid carcinoma (FMTC). Herein, we report a rare mutation of the RET gene (D631Y) in a Turkish family with MEN 2A. The presented case was diagnosed as pheochromocytoma and has got RET gene homozygote mutation, with no clinical evidence of MTC at the time of diagnosis. Four siblings of the patient were asymptomatic and each has got heterozygote mutation of D631Y (c.1891G›T). Three years after bilateral adrenalectomy due to pheochromocytoma, the patient was diagnosed with MTC and underwent total thyroidectomy.

Keywords: Medullary thyroid carcinoma. MEN2A, RET proto-oncogene

From: [1]Department of Medical Genetics, [2]Department of Endocrinology and Metabolism, [3]Department of Pathology, and [4]Department of Otolaryngology, School of Medicine, Mustafa Kemal University, Hatay, Turkey and [5]Department of Endocrinology, Numune Research and Training Hospital, Ankara Turkey.

Correspondence: Dr M Ozsan, Department of Endocrinology and Metabolism, Mustafa Kemal University Medical School, 31001, Hatay, Turkey. Fax: +90 326 2455654;
e-mail: mugeozsan@gmail.com.tr

INTRODUCTION

MEN2A is a rare autosomal dominant disease caused by mutations in the RET proto-oncogene and characterized by medullary thyroid carcinoma (MTC), pheochromocytoma and primary hyperparathyroidism with an incidence of 1 in 200,000 live births. The proto-oncogene RET is composed of 21 exon located on chromosome 10 (10q11.2) and encodes for a transmembrane receptor tyrosine kinase for members of the glial cell line–derived neurotrophic factor family (GDNF). RET gene is expressed on the parathyroid, neural crest (thyroid C cells, brain, parasympathetic and sympathetic ganglion and adrenal medulla) and urogenital systems. Of the cases with MTC, 75% are sporadic and 25% are familial. Patients with MEN2A have a 70% to 100% risk of developing MTC by age 70 years, and MTC is the most important determinant of mortality in these patients (1, 2). The majority of MEN2A and familial MTC cases led to different mutations of ret proto-oncogene in exon 11 and exon 12 (92%). The ret gene and exon 13, 14, 15 have been described non-sense mutations in familial medullary thyroid cancer (1). Herein, we present a case that first presented with pheochromocytoma than MTC with D631Y mutation.

CASE REPORT

A 35-year-old woman referred to our clinic with the clinical suspicion of having MEN 2A syndrome because 3 years ago she had a history of palpitation, hypertension attacks during pregnancy, which ended with a miscarriage. She was diagnosed as pheochromocytoma. I-123 MIBG scan showed bilateral involvement at the adrenals consistent with pheochromocytoma. Her laboratory analysis revealed 24 hours of urine adrenalin: 944μg/day (Normal:0.5-20) noradrenalin: 4314 μg/day (Normal:88-444) metanefrin: 8253 μg/day(Normal:52-341) normetanefrin: 14652 μg/day (Normal:88-444), serum calcium 9.3mg/dl, serum phosphorus

3.17mg/dL (Normal:3.5-4.5), parathormone(PTH) 33.2pg/dl (Normal:12-65), serum calcitonin 26.8 pg/ml(0-11) carcinoembryonic antigen(CEA) 3,26ng/mL(Normal:0-3.8). Bilateral adrenalectomy was performed due to bilateral adrenal adenomas on MRI and bilateral involvement at the adrenals on MIBG. Excised right adrenal measured 6x4.5x2.5cm and left adrenal 4.5x3.5x1cm, which were consistent with pheochromocytoma. She was planned for investigation for multiple endocrine neoplasia but the patient lost follow up. Three years after the adrenalectomy her laboratory analysis showed 24 hour urine metanephrines <10 μg/day, PTH 39.3 pg/dl, serum basal calcitonin 17.3pg/ml, after calcium infusion test calcitonin levels increased to 373 pg/ml at 2 minutes and to 948pg/ml at 5 minutes. Mutation analysis was performed and D631Y homozygote mutation in the RET gene was found. Thyroid ultrasonography revealed two milimetric hypoechoic nodules in the left lobe of the thyroid gland but no abnormal lymph node was detected. Fine needle aspiration biopsy could not be performed because of the milimetric nodules. Bilateral total thyroidectomy with central lymph node dissection was performed on the patient. The pathology was consistent with medullary thyroid carcinoma. DNA was obtained by Qiagen MiniQ DNA isolation kit from all patients' peripheral blood samples. Five patients in this family have got D631Y mutation in the ret gene. The sequence analyses of all patients results confirmed the same mutation in exon 11 and 12 in the ret gene.

RESULTS

A mother was found D631Y homozygote mutation in the RET gene and four siblings were found D631Y heterozygote mutation in the RET gene (Table1). Molecular analysis of exon 11 in the RET gene had been a mutation 631 position that is responsible from GAC to TAC.

The result of pathological examination of the thyroid gland is demonstrated as MTC (Figure 1).

CONCLUSION

MEN2A is a rare and autosomal dominant disease, including different endocrine cancers, which needs early diagnoses for treatment. Two Korean families diagnosed with MEN2A, a novel mutation in codon 631 of exon 11 of the RET gene (D631Y. GAC to TAC) were detected. Two families with 11 individuals are performed ret gene analyses and are detected D631Y germline mutation. Five of those patients had familial MTC, four of them had MEN2A and one of them had familial MTC. Pheochromocytoma was detected in six patients including four patients who had MEN 2A. Two of six patients suffering with pheochromocytoma had no clinical evidence of MTC at the time of diagnosis (2). The pheochromocytoma might be the initial manifestation before the development of MTC in some patients with the D631Y mutation.

Tyer et al. presented an unusual case of MEN2A who has D631Y mutation without medullary thyroid Ca and they described this patient differs from typical clinical manifestations which may be a genetic variant of classic MEN2A syndrome (3). Yao et al. performed ret gene mutation in a Chinese family. They found a novel mutation (deletion) in exon 11 codon 631 and this family has four patients who were consistent with MEN2A phenotype. A family related MEN2A reported first time in codon 631 of exon 11 of ret gene (4). Elston et al. presented a family with the rare RET mutation D631Y in which the proband initially presented with a pheochromocytoma.

In 83% of index patients, pheochromocytoma was the presenting manifestation and only 37% of adult germline mutation carriers have developed medullary thyroid carcinoma.

They showed that patients with a D631Y RET mutation typically present with pheochromocytoma and medullary thyroid carcinoma appear to occur with a later onset than reported in other RET mutations like the present case (5). Beldford et al. described frequent RET gene mutations in sporadic pheochromocytoma and they assessed the pathophysiological mechanism of the RET gene in patients with sporadic pheochromocytomas. They determined new types of molecular defects in RET proto oncogene (D631Y, C634W, M918T) that involve noncysteine residues and loss of exon 10 and these results have a prominent clinical impact for management of patients with presumably sporadic pheochromocytomas (6).

As a conclusion, the clinicians should be vigilant of patients with D631Y mutation, which can be presented with pheochromocytoma first instead of MTC that is different from classic MEN 2A. Prophylactic surgery for MTC in childhood is recommended but there is a need of further data for determining the exact time of the surgery.

REFERENCES

1. Berndt I, Reuter M, Saller B, et al. A new hot spot for mutations in the ret protooncogene causing familial medullary thyroid carcinoma and multiple endocrine neoplasia Type 2A. J Clin Endocrinol Metab 1998;83:770-74.
2. Bae SJ, Kim DJ, Kim JY, et al. A rare extracellular D631Y germline mutation of the RET proto-oncogene in two Korean families with multiple endocrine neoplasia 2A. Thyroid 2006; 16: 609-14.
3. Tyer NM, Braunstein GD, Frishberg D. Unusual case of Multiple Endocrine Neoplasia Type 2A syndrome without medullary thyroid carcinoma. Endocrine Practice 2011;17:4-7.
4. Yao B, Lıu X, Lıang H, et al. A novel mutation (Del631del) of the RET Gene was assoicated with MEN2A in a chinese pedigree. Endocr J 2009;56: 99-104.
5. Eltson MS, Meyer-Rochow GY, Holdaway I, Conaglen JV. Patients with *RET* D631Y mutations most commonly present with Pheochromocytoma and not Medullary thyroid carcinoma. Horm Metab Res 2012; 44:339-342.
6. Beldjord C, Desclaux-Arramond F, Raffin-Sanson M et al. The Ret protooncogene in sporadic pheochromocytomas: Frequent MEN 2-like mutations and New molecular defects. J Clin Endocrinol Metab. 1995; 80:2063-68.

Table1 : Clinical manifestations of the MEN2A patients in this family

Gender	Age at onset	Initial demonstration	MTC	PCC	HPT	Mutation
Female	32 year-old	PCC	++	++	--	D631Y homozygote
Male	5 year-old	--	--	-	--	D631Y heterozygote
Male	8 year-old	--	--	-	--	D631Y heterozygote
Female	11 year-old	--	--	--	--	D631Y heterozygote
Male	12 year-old	--	?	-	--	D631Y heterozygote

PCC: Pheochromocytoma MTC: Medullary thyroid carcinoma HPT: Hyperparathyroidism

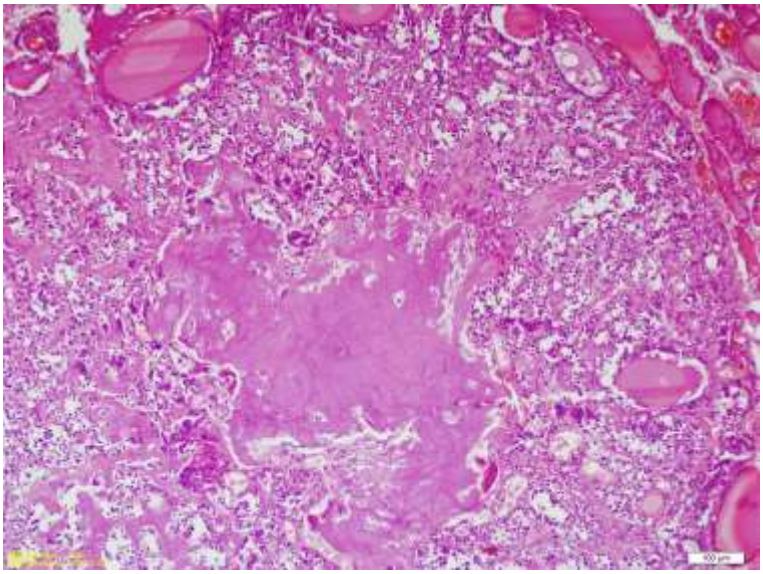

Figure: Microscopic view of medullary carcinoma containing tumor cells with clear cytoplasm and round or vaguely spindled nuclei. Amorphous eosinophilic material (amyloid) deposition was seen in the centre of tumor (Haematoxylin&eosin stain). B14-5842 H&Ex100