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LETTER TO THE EDITOR

Mutation screening of RET proto-oncogene in a family with medullary thyroid carcinoma, marfanoid habitus and pheochromocytoma; from clinically MEN2B to genetically MEN2A syndrome

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Multiple endocrine neoplasia type 2 (MEN2) is sub-classified into three syndromes: MEN2A; MEN2B; and familial medullary thyroid cancer (FMTC). MEN2A is characterized by pheochromocytoma, medullary thyroid carcinoma (MTC), and hyperparathyroidism because of primary parathyroid hyperplasia. MEN2B shares the inherited predisposition to MTC and pheochromocytoma that occurs in MEN2A. However, MEN2B patients typically have a marfanoid habitus (but do not have Marfan's syndrome), mucosal neuromas (typically involving the lips and tongue), and intestinal ganglioneuromatosis.

Pheochromocytoma in MEN 2A is associated most frequently with mutations in codon 634 (in exon 11). Subjects with this have a more than 90, 50, and 30% probability of developing medulary thyroid cancer, pheochromocytoma, and hyperparathyroidism, respectively. MEN 2B is associated with mutations primarily in codon 918 (in exon 16) of the RET proto-oncogene [1, 2]. Differentiation between MEN2A and MEN2B is critical for management of such patients, since, in MEN2A, prophylactic thyroidectomy is recommended to be performed in carriers later. In patients with MEN2B, MTC is often more aggressive and of earlier onset than in MEN2A.

We report here a family in which the index patient had marfanoid habitus, MTC, and bilateral pheochromocytoma which is clinically supposed to be matched with MEN2B and finally diagnosed as MEN2A according to genetic tests.

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The index patient was born to non-related parents of Persian origin, presented with thyroid nodule at the age of 48 years (Fig. 1). His past medical history was unremarkable. He had no history of hypertensive crisis or headache. On physical examination, height and body mass index recorded as 180 cm and 18.1 kg/m^2, respectively. He had marfanoid features including: dolichocephaly, skeletal deformations (pectus excavatum), arachnodactyly with positive thumb sign, decreased upper segment to lower segment (US/LS) ratio, and increased arm span-to-height ratio (More than >1.05).

Fine needle aspiration biopsy was compatible with MTC and preoperational screening for pheochromocytoma was in favor of bilateral adrenal mass. After obtaining informed consent, DNA was isolated from peripheral blood leukocytes using salting out method. Exones 10, 11, 13, 14, 15, and 16 of RET proto-oncogene localized to 10q 11.2 were examined by direct DNA sequencing [3]. This resulted in identification of mutations in Exon 11, codon 634, TGC > CGC (Cystein > Arginine), which was indicative of hereditary MTC, and Pheochromocytoma. This mutation was found in two other daughters and one of his sons, and one of his nephews, too (Fig. 1).

One of his daughters (Fig. 1, Patient 4) had thyroid nodule, and complete evaluations were consistent with MTC. Biochemical and radiological study for pheochromocytoma were against adrenal mass, and total thyroidectomy was performed for her. Total prophylactic thyroidectomy was performed for all the three other RET proto-oncogen carriers.

Bilateral adrenalectomy and then total thyroidectomy were performed for the patient (Fig. 1, index patient). Considering pathology report, pheochromocytoma was intra-adrenal, and no capsular invasion was reported. Microscopic description of thyroid gland was positive for

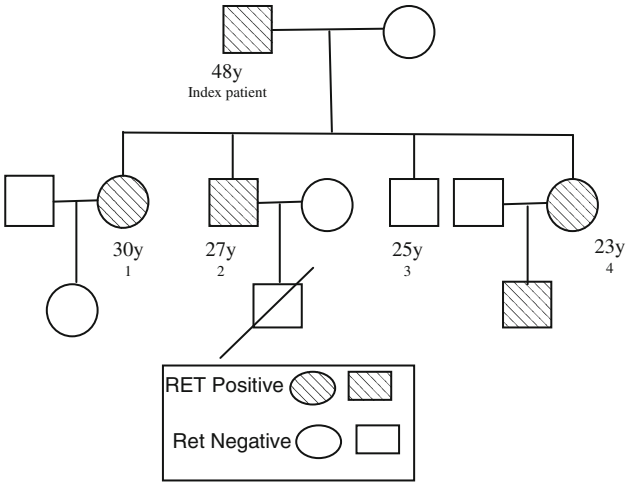

Fig. 1 Genetic relationship of the family diagnosed as multiple endocrine neoplasia type 2

MTC and amyloid deposition, capsular invasion, and lymph node involvement were noted. He was diagnosed with MEN 2 syndrome according to MTC and pheochromocytoma. Evaluation for primary parathyroid hyperplasia was negative in him and his family. In addition, no mucosal neuromas on the lips and tongue were detected. The patient had a marfanoid habitus and clinically was supposed to be matched with MEN2B. No ectopia lentis or aortic abnormalities were reported in evaluations. Unlike patients with Marfan's syndrome, MEN2B patients do not have ectopia lentis or aortic abnormalities, and so marfanoid feature versus marfan syndrome was confirmed. Considering these data, our first diagnosis was MEN2B syndrome—which is actually more aggressive—and, additionally, the absence of hyperparathyroidism was against MEN2A syndrome. On the other hand, genetic evaluation showed mutations in Exon 11, codon 634, which was consistent with a known mutation related to MEN2A. For this codon, the recommended timing of prophylactic thyroidectomy is 2–4 year.

Regarding these findings, marfanoid habitus alone is not a strong clinical finding for categorization of MEN2 subtypes and timing of surgery should be recommended according to genetic evaluation and specific codon.

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Conflict of interest None of the authors.

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