Case Reports

A Case of Multiple Endocrine Neoplasia Type 2B

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A sporadic case of multiple endocrine neoplasia type 2B in a twenty-six year old man who manifested medullary thyroid carcinoma, multiple mucosal neuromas of the tongue and a marfanoid habitus is reported. At the time of diagnosis, he also had multiple liver and lung metastases. Genetic analysis of his lymphocytes revealed a point mutation in exon 16 of the RET proto-oncogene. Since multiple endocrine neoplasia type 2B has a relatively poor prognosis because of the occasional aggressive behavior of medullary thyroid carcinoma, the necessity of the genetic diagnosis of multiple endocrine neoplasia in the early stage is suggested.

Key words: multiple endocrine neoplasia – medullary thyroid carcinoma – marfanoid habitus

INTRODUCTION

Multiple endocrine neoplasia (MEN) is a neoplastic disorder which occurs in multiple endocrine organs. The neoplasia is divided into three categories: MEN type 1, type 2A and type 2B. MEN type 2B is characterized by MTC, pheochromocytoma and mucosal neuromas of the tongue, lips and other sites. Megacolon, diverticula of the gastrointestinal tract and scoliosis have also been reported (1–3). MTC is seen in most cases of MEN 2B, with an earlier age of onset than in MEN 2A (1,4). The progression of MTC in MEN 2B also tends to be more aggressive (5), so early diagnosis using genetic analysis and subsequent prompt treatment are essential for patients with MEN type 2B.

CASE REPORT

CLINICAL HISTORY

A right-sided anterior neck mass was detected in a twenty-six year old man during periodic medical examinations in November 1989 and July 1991. He was referred to the Tokai Hospital and was admitted on August 5, 1991. He appeared lean and tall (Fig. 1A) with full lips (Fig. 1B), which suggested a marfanoid habitus. Multiple tiny nodules of the tongue were also observed (Fig. 1C).

On physical examination, an irregular-shaped, elastic and non-tender mass with an uneven surface, which measured 5 × 4 cm, was palpated on the anterior right side of the neck. Multiple elastic and movable lymph nodes, which measured 4 cm in maximal diameter, were palpable in the bilateral cervical region.

Laboratory data demonstrated a normocytic normochromic mild anemia (Hb 11.7 g/dl) and a serum cholinesterase level of 1400 IU/l. Serum levels of CEA and calcitonin were markedly elevated at 2140 ng/ml and 598 000 pg/ml respectively. Adrenocorticotropic hormone (ACTH) and catecholamine in serum, and VMA (vanillylmandelic acid), 17K-S (17-ketosteroid) and 17OHCS (17-hydroxycorticosteroid) in urine, were all within normal limits.

A chest X-ray showed multiple small nodules, suggestive of pulmonary metastases. Cervical echography revealed a partly calcified mass in the right lobe of the thyroid gland which measured 7.6 × 3.9 cm, and multiple swollen lymph nodes in the cervical region. Abdominal echography showed numerous low echoic lesions with cystic changes and calcification in the liver, suggestive of metastatic lesions. A barium enema elucidated multiple diverticula located in the rectum and the transverse colon.

Bowel obstruction occurred three times after his admission on August 5, 1991, and the follow-up barium enema depicted a stenotic lesion in the descending colon. Panperitonitis was suspected due to left flank pain accompanied by fever and leucocytosis for three days. An emergency laparotomy found panperitonitis caused by the perforation of the diverticulum in the descending colon, and a partial resection of the descending colon was performed on October 12, 1991. The stenotic lesion of the descending colon was caused by the diverticulitis. The patient received two cycles of chemotherapy composed of cyclophosphamide 1000 mg/m² and epirubicin 130 mg/m², but eventually

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Abbreviations: MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; ACTH, adrenocorticotropic hormone.
The patient's appearance with manifestations of marfanoid habitus. B. Full lips. C. Multiple tiny nodules on the tongue.

succumbed to respiratory failure caused by prominent pulmonary metastases, nine months after the operation.

**Pathologic Findings**

Aspiration needle biopsy of the thyroid mass showed atypical cells. The cytological diagnosis was class V, and MTC was suspected.

Microscopic examination of the excised cervical lymph nodes demonstrated tumor cells with granular cytoplasm and large round nuclei, arranged in trabecular fashion in the eosinophilic hyaline material (Fig. 2A). Tumor cells which were clearly demonstrated by argyrophilic stain shown in Fig. 2B were accompanied by material which was positive for amyloid in the stroma. The tumor cells were immunohistochemically positive
Figure 2. A. Microscopic examination of the incised cervical lymph node demonstrates tumor cells with granular cytoplasm and large, round-shaped nuclei, arranged in trabecular fashion in eosinophilic material. B. With Grimelius stain, tumor cells are argyrophilic. C. Tumor cells stain positive for calcitonin (indirect immunoperoxidase). D. Tumor cells stain positive for chromogranin A (indirect immunoperoxidase).
Figure 3. A, Tumor cells stain positive for calcitonin gene-related peptide (indirect immunoperoxidase). B, Amyloid P protein stains positive in the hyaline material, although amyloid AA protein is negative (indirect immunoperoxidase). C, Tongue biopsy: Nodular lesions composed of thickened convoluted nerve fibers are observed in the subepithelial layer.
A case of MEN type 2B

M 1 P N

→

117 bp

71 bp

46 bp

Figure 4. PCR-RFLP analysis of exon 16 of the RET gene. After DNA was extracted from the patient’s lymphocytes, the RET gene was amplified by PCR. The PCR product was digested by Fok I restriction enzyme and electrophoresed in 8% acrylamide gel. The 71 and 46 bp bands are noted in the negative control lane. Only the 117 bp band is observed in the patient’s sample as seen in the positive control lane, because the PCR product is not cut by Fok I. Lane 1 (M), size marker; lane 2 (1), patient; lane 3 (P), positive control (codon 918 ATG→ACG); lane 4 (N), negative control (human placental DNA).

for calcitonin (Fig. 2C), chromogranin A (Fig. 2D) and calcitonin gene-related peptide (Fig. 3A). The hyaline matrix was immuno-histochemically positive for amyloid P protein (Fig. 3B).

Liver biopsy showed that hepatic lesions were immunohistochemically positive for calcitonin and CEA.

In genetic analysis, polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis using DNA extracted from the patient’s lymphocytes elucidated a mutation in codon 918, in exon 16 in the RET gene (Fig. 4). Sequence analysis of exon 10 in the RET gene revealed no mutations in codons 609, 611, 618, or 620 (data not shown). No mutation was noted in codon 634, in exon 11 in the RET gene (data not shown).

DISCUSSION

A disease having MTC, pheochromocytoma and multiple peripheral neuromas was first reported by Williams and Pollack (6). A disease having MTC, pheochromocytoma and multiple peripher-mental length polymorphism (PCR-RFLP) analysis using DNA chemically positive for calcitonin and CEA.

A biopsy of the tip of the tongue showed nodular lesions composed of thickened convoluted nerve fibers in the subepithelial layer, which were diagnosed as mucosal neuromas (Fig. 3C).

Liver biopsy showed that hepatic lesions were immunohistochemically positive for calcitonin and CEA.

In genetic analysis, polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis using DNA extracted from the patient’s lymphocytes elucidated a mutation in codon 918, in exon 16 in the RET gene (Fig. 4). Sequence analysis of exon 10 in the RET gene revealed no mutations in codons 609, 611, 618, or 620 (data not shown). No mutation was noted in codon 634, in exon 11 in the RET gene (data not shown).

Marfanoid habitus, as recognized in our case, is seen in 75% of MEN type 2B (1,9,10), as are skeletal abnormalities such as kyphosis, pectus excavatum and talipes supinatus (3). MTC is seen in approximately 90% of MEN type 2B, and is commonly multiple. This malignant tumor appears in the late teens or twenties (1,4), in contrast with sporadic MTC cases which generally arise rather later in life. According to some reported cases, hyperplasia of C cells of the thyroid (11–13) and hyperplasia of the adrenal medulla (12,14,15) are thought to be premalignant lesions of MTC and pheochromocytoma respectively. In some cases of MTC with dissemination, Cushing’s syndrome (16) and asymptomatic increase of ACTH production (17–19) have been reported. Surgical treatment is the first choice in cases without distant metastases. Patients with distant metastases, as our case, have a poor prognosis. Chemotherapy or irradiation against MTC in MEN type 2B is not effective. The prognosis of MTC in MEN type 2B is poorer than in MEN type 2A or sporadic MCT (5). Our case had multiple lung and liver metastases at the initial diagnosis, and chemotherapy was not effective.

Pheochromocytoma is seen in approximately 50% of MEN type 2B, occurring during the second and third decade of life, and frequently is multicentric and bilateral (1,4,5). In our case, symptoms caused by the elevation of serum catecholamine, such as hypertension, were not noted. Serum and urine catecholamine were within normal levels.

Fifty percent of MEN type 2B are autosomal dominant as the genetic form, the others being sporadic (3). Our case had no particular family history and was thought to be sporadic.

Hofstra et al. (20) reported that the point mutation in codon 664 of the RET proto-oncogene was observed in 9 cases of MEN type 2B. This point mutation causes the conversion of the 918th methionine (ATG) to threonine (ACG) in the tyrosine kinase domain. Carlson et al. (21) reported that the same point mutation was observed in 18 families of autosomal dominant pedigree and in 16 sporadic cases. The same point mutation was reported in other series (20,22,23), in Japan (23), and in one of 12 cases of sporadic pheochromocytoma (22).

In MEN type 2A and familial MTC, mutation of the RET gene happened in codons 609, 611, 618, 620 and 634, which code cysteine in the 5-side of the transmembrane domain. This mutation is concentrated especially in codon 634. Patients having this mutation tend to have pheochromocytoma (24). The expression of the activated RET was noted in 25% of papillary thyroid carcinoma cases (25). This fact is of great interest in view of the relation between the activated RET gene and oncogenesis.

Based on our experience, we suggest that genetic analysis may be useful in the early diagnosis and treatment of MEN type 2A, 2B and familial MTC carriers.

References


