A Case of Multiple Endocrine Neoplasia Type II b: Endocrinological Evaluation and Family Screening

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Abstract

The case of a 27 year-old woman with typical manifestations of multiple endocrine neoplasia type II b is reported. Medullary carcinoma of the thyroid was detected on the occasion of an operation for goiter when she was 22 years of age. Constipation due to megacolon caused by intestinal neuroma had persisted since childhood. Neuroma of the tongue and lips, hypertrophic corneal nerve and Marfanoid habitus were also found. The presence of pheochromocytoma was suggested in view of the positive cold pressor and results of glucagon loading tests, but this remains inconclusive. There was prolonged and exaggerated response of growth hormone and luteinizing hormone after provocative tests for anterior pituitary gland, in spite of normal basal levels. Screening of her family members for medullary carcinoma of the thyroid was carried out by measurement of immunoreactive calcitonin. Two siblings were shown to be hypercalcitoninemic, presumably due to occult medullary carcinoma of the thyroid. This case appeared to be the first in Japan showing multiple endocrine neoplasia type II b accompanied by familial hypercalcitoninemia.

Multiple endocrine neoplasia (MEN) syndromes are rare disorders which represent multifocal, hormone-secreting neoplasias of endocrine organs in definite combinations. They are classified into two types; MEN type I (Wermer syndrome), which consists of pituitary, pancreatic islet and parathyroid tumors, and type II, involving the parathyroid, thyroid C-cell and adrenal medulla. Recent awareness of a variant form of type II (Williams and Pollock, 1966; Schimke et al., 1968; Gorlin et al., 1968; Baum and Adler, 1972; Khairi et al., 1975) composed of multiple mucosal neuroma in addition to pheochromocytoma and medullary carcinoma of the thyroid (MCT), led to subclassification of the syndrome into type II a (usually referred to Sipple syndrome) and type II b (or type III, mucosal neuroma phenotype MEN). The diseases are occasionally transmitted through an autosomal dominant mode of inheritance. We have encountered a case of typical MEN type II b and evaluated her endocrinological status by various provocative tests for thyroid, parathyroid, adrenal medulla and cortex, pituitary and pancreatic islet. At the same time, her family members were screened with stimulation tests for thyroid C-cells (Starling...
Measurement of plasma calcitonin

Plasma levels of immunoreactive calcitonin (iCT) were measured by radioimmunoassay. Synthetic human calcitonin was kindly supplied by Ciba Geigy Ltd. (Basle, Switzerland) and was used as assay standard. Rabbit antiserum against calcitonin was obtained by several injections of synthetic human calcitonin coupled to bovine serum albumin. Final dilution of antiserum was 1:150,000. Radioiodination of calcitonin was performed by the chloramine-T method. Basal level of plasma iCT in normal subjects ranged from undetectable (lower limit of sensitivity of assay was 48 pg/ml) to 150 pg/ml. Intra- and interassay variations were 5% and 7.2%, respectively.

Proband

M.Y., a 27 year-old single female, kindergarten teacher, was admitted to the Third Division, Department of Medicine, Kobe University Hospital in August 1978, because of attacks of palpitation with finger-tip pallor. Since childhood, she always had had to use laxatives for constipation, and the diagnosis of megacolon was made at the age of 15. In 1974, at the age of 22, she consulted a surgeon for megacolon. Biopsy from rectal mucosa showed neuromata of the rectum and anorectal myectomy was performed for megacolon. Nodular goiter was pointed out at the same time and following the diagnosis of thyroid cancer, total thyroidectomy with removal of regional lymph nodes was performed successfully without significant complication during and after operation.

Histological studies revealed MCT (Fig. 1-a) and calcitonin-containing tumor cells were detected by means of an immunohistochemical technique (peroxidase-antiperoxidase method; Fig. 1-b). In 1976, small painful nodules appeared on her tongue and hard palate, and the diagnosis of neuroma was made on biopsy. In the summer of 1977, she experienced brief episodes of palpitation with finger-tip pallor, which occurred twice or more monthly. She consulted our out-patient clinic for the evaluation of the attack. Desiccated thyroid had been administered for postoperative hypothyroidism. Menstruation was regular. In her family history, her paternal grandmother and father had died of uterine cancer and hepatoma, respectively. Her maternal grandmother had suffered from hypertension and rheumatoid arthritis.

Physical examination revealed a young woman of 155 cm in height and 49 kg in weight with pectus excavatum, pes cavus and arachnodactyly. Blood pressure was 106/80 mmHg and pulse rate 84/min, regular. The patient showed bumpy lips and small nodules on the anterior surface of the tongue (Fig. 2), the buccal mucosa and the hard palate. She also had white striae in the lower eyelids, which was identified as hypertrophy of corneal nerves by slit lamp examination. There was no tumor mass in the neck, the axilla or the abdomen. Urinalysis was negative for protein, sugar and sediment. Routine laboratory findings were as follow; RBC 418 × 10⁴/mm³, WBC 5000/mm³ with normal differential counts, platelets 24.5 × 10⁴/mm³, total protein 7.3 g/dl, albumin 4.5 g/dl, GOT 19 K.U., GPT 6 K.U., alkaline phosphatase 1.3 mMU (Bessey-Lowry unit) cholesterol 194 mg/dl, creatinine 0.3 mg/dl, Na 136 mEq/l, K 4.7 mEq/l, Cl 102 mEq/l, Ca 7.4 mg/dl, P 5.9 mg/dl, %TRP 99.1%, TmPO₄/GFR 8.6 mg/dl, CEA 1.2 ng/ml. Chest and skull x-rays were unremarkable. Thyroid function tests showed low normal values (T₃ RSU 25.2%, T₄ 4.2 µg/dl). The basal level of iCT was still high (510 pg/ml) and significant elevation of iCT over 10 ng/ml was seen after a pentagastrin loading test (0.5 µg/kg B.W., bolus injection) and rapid calcium loading test (4 mg/kg B.W., in 1 min) (Fig. 3). Plasma levels of immunoreactive parathyroid hormone (c-PTH), using antibody mainly recognizing carboxy-terminus, were undetectable during an EDTA loading test. Twenty-four hour
Fig. 1-a. Histological picture of the thyroid carcinoma of the proband. Spindle-shaped tumor cells, having eosinophilic cytoplasm are trabecular in arrangement without formation of gland or follicle (H-E stain ×100).

Fig. 1-b. Immunohistochemical staining of the thyroid carcinoma. Tumor cells contain fine granules, positive for calcitonin (peroxidase-antiperoxidase method, ×400).

Urinary excretions of adrenaline and noradrenaline were 26.0 μg and 12.2 μg, respectively. In order to determine whether or not the attack of palpitation is due to pheochromocytoma, provocative tests for the adrenal medulla were performed. A cold pressor test yielded a positive response and a glucagon loading test (1 mg) resulted in the elevation of blood pressure and a slight increase in urinary excretion of adrenaline and noradrenaline. Although adrenal scintigram, using 131I Ad-}

ersterol, revealed no space-occupying lesion in bilateral adrenal glands, computed axial tomographic scanning of the abdomen disclosed slight enlargement of the left adrenal gland. Angiography showed a normal right adrenal artery, but failed to detect that on the left. Urinary excretion of 17-OHCS and 17-KS averaged 7.3 and 9.0 mg/day, respectively, and the diurnal rhythm of the plasma cortisol level showed a normal pattern. Examination of pituitary function by thyrotropin-releasing
hormone (TRH; 500 µg), luteinizing hormone-releasing hormone (LH-RH; 100 µg) and insulin (0.1 U/kg B.W.) loading yielded a normal response of cortisol, thyrotropin (TSH) and follicle stimulating hormone (FSH). Basal levels of growth hormone (GH) and luteinizing hormone (LH) were normal (4.8 ng/ml and 8.5 mIU/ml, respectively), but the patient showed prolonged and exaggerated response of plasma levels of GH and LH, up to 65 ng/ml and 129 mIU/ml, respectively, to provocative agents (Fig. 4). Serum glucose and immunoreactive insulin (IRI) values were normal during an oral glucose tolerance test. The
plasma serotonin value was 80.4 µg/dl (normal range 10-30 µg/dl) and urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) was 3.5 µg/day (normal range 1.6-6.4 µg/day).

**Family Screening**

Plasma iCT of her family members (Fig. 5) was measured by radioimmunoassay. Five members, including her mother, three elder brothers and one younger sister, were ex-
has been reported, this possibly does not play any role in this patient without evidence of pheochromocytoma or calcitonin-producing tumor other than MCT. In addition, exaggerated responses of plasma iCT to provocative agents presumably indicate secretion of authentic calcitonin from thyroid C-cells.

When surgical treatment is considered for MEN syndrome, it is most important to determine whether or not pheochromocytoma is present, because pheochromocytoma may release excessive amount of catecholamines under surgical stress such as thyroidectomy, even in the absence of typical symptoms or biochemical changes under normal circumstance. Dembrow (1977) reported a case of MEN type II b showing unexpected hypertensive crisis on the way down to the operating room for thyroidectomy. Khairi et al. (1975) found 19 cases of pheochromocytoma among 41 patients with mucosal neuroma phenotype MEN (46.3%) in his detailed review of the literature. Chong et al. (1975) investigated 137 cases of MCT and reported 5 patients with simultaneously pheochromocytoma among 14 cases of MEN type II b (35.7%). Since our patient underwent thyroidectomy uneventfully, she probably had no clinically active pheochromocytoma at that time. In view of the possible appearance of pheochromocytoma in

Discussion

Our case fulfills the criteria of MEN type II b; multiple mucosal neuroma and histologically proven MCT, with characteristic body habitus, i.e. pectus excavatum, pes cavus and arachnodactylyia. It was not possible to confirm the presence of pheochromocytoma by angiography, adrenal scintigra phy or computed axial tomographic scanning of the abdomen, despite various provocative tests suggesting its possibility. Recurrence of MCT was suggested by a high level of plasma iCT, although attempts to detect precise localization of metastatic or recurrent lesion failed. Although ectopic secretion of iCT from pheochromocytoma (Heath and Edis, 1979) or other malignant neoplasias (Samaan et al., 1980; Silva et al., 1979; Schwartz et al., 1979)
the future, careful follow up is mandatory.

Hypocalcemia, hyperphosphatemia with elevated maximal threshold of phosphate excretion (TmPO4/GFR) and undetectable c-PTH levels during EDTA loading test indicate hypoparathyroidism following radical thyroidectomy.

In addition to typical manifestation of MEN type II b, provocative test for anterior pituitary gave rise to peculiar responses. An early pituitary involvement, such as hyperplasia of GH and/or LH secreting cells might be present as part of the overlapping syndrome between MEN type I and II (Berg et al., 1976; Hansen et al., 1976; Tateishi et al., 1978; Cameron et al., 1978; Nathan et al., 1980). Because the prevalence of MEN type II b is smaller than that of type II a, only a few reports of MEN type II b which overlap with MEN type I are found.

Family screening disclosed that the two siblings, at least, have hypercalcitoninemia. In general, high levels of plasma iCT are seen in subjects with calcitonin-producing tumor, especially MCT, lung cancer, breast cancer etc. and chronic renal failure. Familial hypercalcitoninemia found in three of six members including the proband suggests that there may be occult MCT in the second elder brother and the younger sister. In the second brother, the responses of plasma iCT to provocative agents were not as typical as that of the proband, so that the presence of occult MCT in this subject remains inconclusive. Her younger sister showed mild elevation of iCT levels after pentagastrin loading and calcium infusion. Such familial occurrence of hypercalcitoninemia along with a typical case of MEN type II b strongly suggests the presence of occult MCT or C-cell hyperplasia (Wolfe et al., 1973). In Japan, 5 cases of MEN type II b were reported (Watanabe et al., 1968; Sakamoto et al., 1974; Nakano et al., 1977; Katoh et al., 1978; Morimoto et al., 1980) up to 1980. The record of the operation for our proband has already been reported by Katoh et al., with histological findings. All the other 4 cases, however, appear to be sporadic in occurrence. This patient therefore appears to be the first case of MEN type II b with a family history of hypercalcitoninemia in Japan. The usefulness of the measurement of plasma iCT and pentagastrin test in detecting occult MCT among high risk members has been stressed by many authors. The two siblings with hypercalcitoninemia were found apparently healthy when they underwent a physical examination. This case thus illustrates the importance of family screening with measurement of plasma iCT and calcitonin provocation tests in a case of apparently sporadic MCT.

References

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