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Three Cases in Two Families of Multiple Endocrine Neoplasia (MEN) Type IIa*)

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ABSTRACT

We have experienced 3 cases in 2 families of multiple endocrine neoplasia (MEN) type IIa. Case 1: 61 year-old female underwent her first operation of right hemithyroidectomy for thyroid cancer followed by her second of right adrenalectomy later added thereto for pheochromocytoma as diagnosed. In the meantime, her cousin was found to have undergone an operation at another hospital for the same disease. She was further diagnosed as medullary carcinoma of thyroid gland (MCT) in her left thyroid gland and a total thyroidectomy was performed. Case 2 : 33 year-old female had a chief complaint of palpitation and was introduced to our 2nd Department of Surgery for suspection of pheochromocytoma. It was found to be of MEN type IIa after various tests. Bilateral adrenal glands of pheochromocytoma were removed followed by a total thyroidectomy performed 47 days later. In the family study of case 2, MCT was detected in her eldest brother and identified as familial type. This case 3, 49 year-old male had no parathyroid disease or pheochromocytoma and total thyroidectomy was performed for MCT.

INTRODUCTION

In 1932, Eisenberg[8] first reported the combination of pheochromocytoma and thyroid cancer. It was initially considered an accidental combination. In 1961, Sipple[15] who collected the records of 538 cases of pheochromocytoma reported 6 cases of its combination with thyroid cancer. In 1965, Williams[18] pointed out that thyroid cancer was of medullary type often occurring to the same family and usually involving hyperparathyroidism. This disease called Sipple's syndrome has come to be named MEN type II, while Wermer's syndrome is called MEN type I. In 1975, however, Block et al.[2] presented the cases relatively rarely involving parathyroid disease but often involving pseudo-mucosal neuroma or Marfan state, as a subordinate type to MEN type II. From this point, it was proposed to call the conventional MEN type II was called type IIa (or type II) and pseudo-mucosal neuroma involved syndrome was named type IIb (or type III).

CASE REPORTS

Case 1: 61 year-old female

She felt struma in 1964, was attacked by palpitation and headache at times since then and hospitalized on June 19, 1974. On July 16, a right hemithyroidectomy with modified radical neck dissection was performed. There were 2 tumors of 3.2×2.3 cm and 1.3×1.0 cm in size found in the right thyroid gland. The pathological finding was MCT. In, 1978 and May 1979, she felt hypertensive and back pain attacks. In September 1980, her cousin underwent a Sipple's syndrome operation at another hospital. On October 6, she was diagnosed again at our 2nd Department. High values of adrenaline (Ad) and noradrenaline (NAd) were indicated in blood test. On November 17, she was rehospitalized for suspition of pheochro-

*) 岸　直彦, 西亀正之, 天野国幹, 武市宣雄, 松山敏哉, 江崎治夫：MEN type IIa を呈した2家系3症例の経験

Table 1. Case 1 Pre and Postoperative Laboratory Data

		Preoperative	Postoperative	(normal)
Serum:	Adrenaline	0.3	0.02	(≦0.12 ng/ml)
	Noradrenaline	1.23	0.23	(0.06-0.45 ng/ml)
Urine:	Adrenaline	100↑	16.4	(3-15 μg/day)
	Noradrenaline	422.2	96.8	(26-121 μg/day)
	VMA	18.0	9.5	(4.7-11.4 mg/day)
Serum:	CEA	3.3	—	(≦2.5 ng/ml)
	calcitonin	0.24	—	(≦0.3 ng/ml)
	PTH	0.2↓	—	(≦0.5 ng/ml)
	calcium	4.3	4.6	(4.3-5.5 mEq/liter)

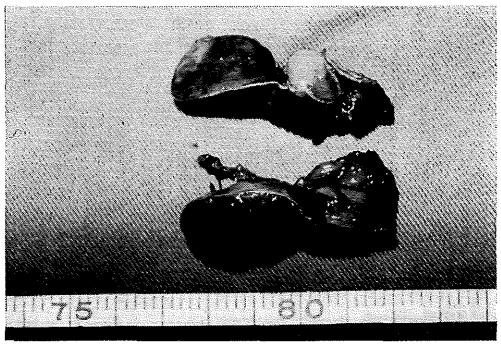

Fig. 1. Extirpated pheochromocytoma of Case 1

mocytoma.

As a results of the laboratory data, she was diagnosed as pheochromocytoma of the right adrenal gland, as shown in Table 1. On December, a right adrenalectomy was performed by the right flank incision. Fig. 1 shows the excised specimen. Two tumors of 2.6×1.7 cm and 1.4×0.9 cm were observed. No complication was observed after operation and serum Ad and NAd returned to normal. She left the hospital on December 27. In a follow-up, her serum calcitonin showed a high value of 0.409 ng/ml, when a tumor of 1.8×1.0 cm was palpated in her left thyroid gland. MCT was suspected by aspiration biopsy cytology (ABC). On February 10, 1981, she was hospitalized to complete a total thyroidectomy by adding the left hemithyroidectomy. The tumor, 1.5×1.0 cm in the left thyroid gland, was pathologically diagnosed as MCT. No metastasis to lymphnodes was observed. After operation, she is being followed up under replacement therapy using thyroid hormone.

Case 2: 33 year-old female

In February 1980, she was suddenly attacked by palpitation and headache 3 days after delivery of her 4th child. The attacks recurred 4-5 times a day since then. For the purpose of examination for her syndrome, she consulted her near doctor where she was received conservative therapy due to unknown cause. In July 1982, high catecholamine value were observed at another hospital and introduced to our clinic under the suspicion of pheochromocytoma. She was admitted in our clinic on August 25. Her blood pressure was 124/80 mmHg at rest rose to 250/120 mmHg at time of attack. The attack recurred 5-15 times a day. Alpha and β-bloker YM09538 ($\alpha > \beta$) had been administered till the day before the operation starting from 20 mg/day ending 40 mg/day. Based on the laboratory data as shown in

Table 2. Case 2 Pre and Postoperative Laboratory Data

		Preoperative	Postoperative	(normal)
Serum:	Adrenaline	2.37	almost 0	(≦0.12 ng/ml)
	Noradrenaline	11.31	0.40	(0.10-0.41 ng/ml)
	Cortisol	12.8	5.4	(3.7-13.0 μg/dl)
	ACTH	—	141	(10-90 pg/dl)
Urine:	Adrenaline	69.57	0.35	(3-15 μg/day)
	Noradrenaline	192.76	5.76	(26-121 μg/day)
	VMA	4.09	0.17	(1.8-9.0 mg/day)
	17-KS	3.2	1.49	(4-8 mg/day)
	17-OHCS	3.7	5.6	(1.5-4.0 mg/day)
Serum:	CEA	2.2	1.1	(≦2.5 ng/ml)
	Calcium	4.7	4.5	(4.3-5.5 mEq/liter)
	Calcitonin	0.5	0.1	(≦0.3 ng/ml)
	PTH	0.6	0.3	(0.2-1.3 ng/ml)

Table 2 and the localized examination, pheochromocytoma on her bilateral adrenal gland was examined. On September 30, the first operation was performed. Laparotomy by upper abdominal transeverse incision was performed to removal of the tumors. The right side tumor was 7.5×5.0 cm in size and weighing 132 g and the left side, one was 2.0×2.0 cm and the other was 3.0×5.0 cm and total weighing 60 g.

After the operation, the steroid hormone replacement was performed. This patient had been palpated thyroid tumor in right lobe at the time of admission and diagnosed as MCT by laboratory data and ABC as shown in Table 2. Fig. 2 shows the ABC findings. After all, the patient was proved to be Sipple's syndrome, MEN type IIa. On November 16, MCT was operated by total thyroidectomy and two tumors were observed, one was 1.0×0.5 cm and the other was 0.3×0.2 cm. Fig. 3 shows the excised specimen. After the operation, the patient is being followed up under thyroid hormone replacement and administration of anti-cancer agent.

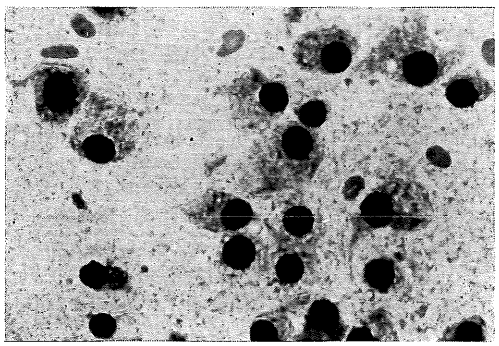

Fig. 2. Aspiration Biopsy Cytology of Medullary thyroid carcinoma of Case 2. Circular nucleus dispersed in round cell body. Small granules observed in cytoplasm.

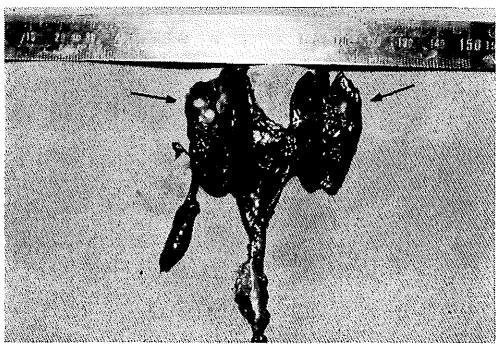

Fig. 3. Extirpated thyroid gland. (Case 2) Multiple MCT were observed (arrow).

Case 3: 49 year-old male

The family study of case 2 was conducted using an outpatient. The eldest brother of case 2 was examined and his serum catecolamine was measured, as shown in Table 3. His serum calcitonin value was as high as 3.2 ng/ml. A tumor in a bean size was palpated at the left thyroid gland. MCT was diagnosed by ABC. He was hospitalized on February 4, 1982. The parathyroid gland and pheochromocytoma were not suspected by laboratory data yet. On February 17, a total thyroidectomy was performed for MCT. Two tumors were observed at the right thyroid gland of 0.7 and left side thyroid gland of 0.5 cm in diameter. As his serum calcium was lowered after the operation, calcium lactate and α-D_3 were administered. During this hospitalized period, no abnormal episode in blood pressure, etc., was observed.

Table 3. Case 3 Preoperative Laboratory Data

		Properative	(normal value)
Serum:	Adrenaline	0.06	(≦0.12 ng/ml)
	Noradrenaline	0.45	(0.10-0.41 ng/ml)
Urine:	Adrenaline	16.60	(3-15 μg/day)
	Noradrenaline	62.9	(26-121 μg/day)
Serum:	Calcium	4.7	(4.3-5.5 mEq/liter)
	PHH	0.2	(0.2-1.3 ng/ml)

DISCUSSION

Sasano et al.[14] have reported the MEN cases in Japan as familial and non-familial cases. The former includes 25 cases of type I in 6 families, 111 cases of type IIa in 26 families and none of type IIb; and the latter, 34 cases of type I and 30 of type IIa and 6 of type IIb; respectively. MCT and pheochromocytoma and parathyroid disease belong to MEN type IIa with their frequency of ocurrence of 70%, 79% and 54%, respectively, as reported[19]. On the other hand, of all MCT cases, 20%[5] belongs MEN; of pheochromocytoma, 6%; and of paratxyroid disease, 8.5%[10] or 15%[6]; according to another report. In our clinic, 3 of 6 MCT cases and 2 of 7 pheochromocytoma cases

belonged to MEN.

Also reported are some MCT cases belonging to MEN which produce prostaglandin with diarrhea observed and which produce ACTH with Cushings syndrome[1,11]. Pheochromocytoma has already been reported[13]. The characteristics of phecchromocytoma in MEN are said as generally adrenaline priority, presence of tumor in bilateral adrenal gland in many cases[4,7] and hypertention is rather attacktic type than of continuous type.

The principle of surgical therapy for MEN type IIa is that two operation are ruquired for pheochromocytoma, if any. In case 1, since various tests including ABC have not yet been established, the patient had severe variation in blood pressure during the initial operation and was attacked by severe hypertention immediately after operation. It means that the operation had been performed under very risky condition. In cases of MCT and parathyroid disease, it is necessary to investigate the presence of pheochromocytoma by performing frequent measurement of blood pressure, measurement of catecholamine in serum and further various infusion tests. Pheochromocytoma is often found in bilateral adrenal gland, in which case a total adrenalectomy will be performed[12]. As in case 2, in which tumor is well capsulated, it will be possible to leave a part of normal adrenal gland, provided no malignancy must be confirmed with a frozen section examination, not to mention. In case 2, after termination of the steroid hormone replacement therapy after the operation, the function of adrenal cortex was found remaining although a little, as a result of serum cortisol, urine 17-KS, 17-OHCS and rapid ACTH infusion test, and there was no special patient's complaints observed. Since it is difficult to control the steroid hormone replacement therapy after total adrenalectomy, the hemi-adrenalectomy may be performed provided tumor is confirmed for being present on one side only and careful follow-up is performed after the operation[17]. As to MCT, multiple tumors are observed almost in all cases including C-cell hyperplasia, the total thyroidectomy will be positively performed because of many deaths of MEN type IIa caused by MCT and because of relatively easy thyroid hormone replacement therapy to be performed after total thyroidectomy. For parathyroid disease, 2 methods are available: the subtotal parathyroidectomy in which a half of gland is exised leaving 3 glands and the auto-transplantation of a part of gland after the total parathyoidecetomy[9]. In practice, it may be difficult to confirm the normal parathyroid gland during operation. The main causes of death of MEN type IIa is by MCT and due hypertensive crisis of pheochromocytoma. In general, the 5-year survival rate of MCT is said to be 50-80%[5,16], but MEN type IIa to show relatively better prognosis of MCT than type IIb[3,16]. As in case 3, many cases are diagnosed in the early stage in family study. Considered MEN type IIa even if either disease of MCT or pheochromocytoma is diagnosed, a creful family study to be performed may provide a possibility for better prognosis of MEN.

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