A Case of Extraadrenal Pheochromocytoma Associated with Adrenal Cortical Nodular Hyperplasia and Papillary Thyroid Carcinoma

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Abstract. A 64-year-old woman was admitted in November, 1996 for fluctuating blood pressure. There was multinodular goiter in her neck. High urine VMA and serum aldosterone were noted. Computed tomography showed an oval lesion in the left adrenal gland. Left adrenalectomy was performed and the pathology was proved to be adrenal cortical nodular hyperplasia. Fluctuating blood pressure and high urine VMA persisted after the operation. CT scan of the abdomen revealed a soft tissue mass in lower abdomen. The patient was admitted again in September, 1997. Laboratory examinations showed normal serum aldosterone, normal plasma renin activity and high urine VMA. Aspiration cytology of the thyroid gland disclosed papillary thyroid carcinoma. [-131I]-metaiodobenzylguanidine image revealed a high uptake lesion in the right L-3 paravertebral area. Tumor excision and thyroidectomy were performed. The pathology was reported as extraadrenal pheochromocytoma and papillary thyroid carcinoma. Papillary thyroid carcinoma is rarely associated with pheochromocytoma. To our knowledge, this paper is the first report of a patient with extraadrenal pheochromocytoma associated with papillary thyroid carcinoma and adrenal cortical nodular hyperplasia.

Key words: Extraadrenal pheochromocytoma, Thyroid papillary carcinoma, Adrenal cortical nodular hyperplasia, Adrenal incidentaloma

PHEOCHROMOCYTOMA is a catecholamine-producing tumor that arises from the chromaffin tissue. It is estimated that pheochromocytoma occurs in 0.1% to 0.2% of all patients with hypertension in the United States [1]. Pheochromocytoma may be familial in 10% of patients. The familial tumors may occur in association with a variety of other conditions. Association of medullary thyroid carcinoma with pheochromocytoma is well known in multiple endocrine neoplasia type 2A (MEN 2A, Sipple’s syndrome) [2]. Papillary thyroid carcinoma is only rarely associated with pheochromocytoma [3-12]. The coexistence of pheochromocytoma and adrenocortical abnormalities has been reported. Inoue et al. [13] reviewed the literature and concluded that most of the cortical abnormalities were hyperplasia, with manifestations of Cushing’s syndrome due to ectopic ACTH production by the pheochromocytoma. To our knowledge, we present the first case of extraadrenal pheochromocytoma associated with adrenal cortical nodular hyperplasia.
associated with papillary adenocarcinoma of the thyroid gland and adrenal cortical nodular hyperplasia.

Case Report

A 64-year-old female first visited Taiwan Provincial Taipei Hospital (TPTH) with complaints of dizziness and exertional dyspnea in June, 1995. She had a history of hypertension for more than 2 years. Labile blood pressure (80/60 to 200/110 mmHg) and multinodular enlargement of the thyroid were noted. Her biochemistry studies were normal, but her hemogram revealed hemoglobin (Hb) 8.6 g/dL. Further survey was not performed due to poor compliance. The symptoms of episodic sweating, palpitation and fainting gradually worsened, and she was admitted in November, 1996 suspected of having a pheochromocytoma.

The patient weighed 56 kg and her height was 152 cm. During admission, her blood pressure fluctuated from 80/50 to 220/120 mmHg. The findings on physical examination were unremarkable except for multinodular enlargement of the thyroid. Her family history was non-contributory.

The laboratory studies showed Hb 11.5 g/dL, fasting blood glucose 113 mg/dL, serum potassium 3.7 mmol/L, glutamic-oxalacetic transaminase (GOT) 44 IU/L, carcinoembryonic antigen (CEA) 3.3 ng/mL (normal range 0.2-5.0 ng/mL). The endocrinological examinations revealed serum levels of T3 140 ng/dL (normal: 82-170 ng/dL), T4 10.5 µg/dL (normal: 4.5-12.5 µg/dL), TSH 0.53 µIU/mL (normal: 0.4-4.0 µIU/mL), PRL 8.5 ng/mL (normal: 1.8-20 ng/mL), aldosterone 288 pg/mL (supine reference range: 12-150 pg/mL), T3 120 ng/dL, T4 11.3 µg/dL, TSH 0.82 µIU/mL, serum aldosterone 137 pg/mL, plasma renin activity 1.5 ng/mL/h (supine reference range: 0.15-2.33 ng/mL/h), 0800 h cortisol 18.7 µg/dL, 1600 h cortisol 10.0 µg/dL, calcitonin 72.9 pg/mL, and urine VMA 19.7 mg/24 h. Papillary thyroid carcinoma was proved by aspiration cytology. [131I]-metaiodobenzylguanidine (MIBG) scan revealed a tumor of high MIBG uptake in the L-3 paravertebral area on the right side. The pituitary CT scan was negative. She was then referred to National Taiwan University Hospital (NTUH) for surgery with the impression of extraadrenal pheochromocytoma and papillary thyroid carcinoma.

Endocrine survey at NTUH showed serum ACTH 39.2 pg/mL (normal: <50 pg/mL at 0800 h), cortisol 10.5 µg/dL, plasma aldosterone 136 pg/mL, plasma renin activity 0.12 ng/mL/h, urine VMA 18.2 mg/24 h, epinephrine 11.8 µg/24 h (normal: <20 µg/24 h), norepinephrine 514 µg/24 h (normal: <80 µg/24 h), dopamine 245 µg/24 h (normal: <440 µg/24 h). Magnetic resonance imaging (MRI) of the abdomen revealed a 6 x 5 x 4 cm lobulated mass lesion in the right periaortic area at the infrarenal level. Periaortic tumor excision, cholecystectomy and bilateral thyroidectomy were performed. The resected
**Fig. 1.** (A) CT image of adrenal glands. An oval hypodense lesion (arrow) without enhancement after administration of contrast medium was noted over the left adrenal gland. (B) The gross appearance of the resected left adrenal gland. Small and large nodular lesions are seen on the surface. (C) The cut surface of the left adrenal gland. There are small (short arrow) and large (long arrow) nodular lesions on the cortex. Large nodular lesions approach the center. (D) Microscopic features of the left adrenal nodules. Nodular hyperplasia of the cortex is present. (H.E. stain, ×100).

**Fig. 2.** (A) Microscopic features of the resected periaortic pheochromocytoma. The tumor is composed of nests of large cells separated by well-vascularized stroma. (H.E. stain, ×200). (B) Immunohistochemistry stain of the pheochromocytoma. The chromogranin A stain is positive. (× 200).
periaortic tumor was 4.5 x 4.5 x 4 cm in size and 52 g in weight. Grossly the specimen had a variegated appearance with yellow, grey and brown foci with areas of necrosis and hemorrhage. Microscopically the pheochromocytoma (Fig. 2A) was composed of nests of large cells separated by well-vascularized stroma with central infarction. Some of the cells had large bizarre hyperchromatic nuclei. Capsular invasion was seen but there was no evident tumor embolus. Immunohistochemistry chromogranin A stain was positive (Fig. 2B) and that of ACTH was negative. The specimen of the thyroid glands contained a 0.7 x 0.4 cm well-defined white nodular lesion in the right lobe and a 2.0 x 1.5 cm ill-defined white fibrotic nodule in the left lobe. Microscopically the right lobe of the thyroid showed signs of nodular hyperplasia and the left lobe revealed papillary carcinoma with focal sclerosis. There was no evidence of c-cell hyperplasia or medullary carcinoma in either thyroid. Immunohistochemistry stain of the thyroid was negative for calcitonin. The removed gall bladder showed changes due to chronic cholecystitis. The postoperative course was uneventful and the blood pressure remained stable without medication. The patient received 100 mCi $^{131}$I radioiodine eradication one month later and remained well thereafter with thyroid hormone replacement.

Discussion

We have described a case of pheochromocytoma associated with papillary thyroid carcinoma and adrenal cortical hyperplasia. The association between papillary thyroid carcinoma and adrenal or extraadrenal pheochromocytoma is rare [3–12]. In reviewing 526 Japanese patients with pheochromocytoma, Sato [14] reported that 3 patients (0.57%) had papillary thyroid carcinoma. Matsuo et al. [15] reported that 2 out of 120 autopsied cases with pheochromocytoma had non-medullary thyroid carcinoma. Parry et al. [16] reported 4 cases of non-medullary thyroid carcinoma out of 222 patients with carotid body paraganglioma. In their review, Oishi et al. [12] reported that among nine patients with pheochromocytoma associated with papillary thyroid carcinoma, eight were female and one was male. The ages of the patients ranged from 31 to 65 years old (56.2 ± 9.6 yr, Mean ± SD). Three of the patients had extradural pheochromocytoma and two patients had bilateral adrenal pheochromocytoma. One of the patients had coexistence of MEN 2A (medullary thyroid carcinoma, bilateral pheochromocytoma) and papillary carcinoma of the thyroid.

The association of thyroid carcinoma in patients with pheochromocytoma is 14 times greater than in the general population. The increased incidence might be due to the fluctuating thyrotropin secretion caused by circulating catecholamines [2]. Pheochromocytomas are capable of producing and secreting a number of peptides such as insulin-like growth factor II [17], hypothalamic-like and pituitary-like hormones [18]. Those biological substances may cause the development and/or growth of the papillary thyroid carcinoma. Genetic factors might also play a part in the association of the two tumors. The ret protooncogene locus, shown to be structurally rearranged in human papillary thyroid cancers [19], has tight linkage to the MEN 2A locus [20]. Concurrent medullary and papillary carcinomas of the thyroid gland have been reported [21–24]. Decker [25] concluded that the expression of papillary thyroid carcinoma in MEN 2A may be due to the presence of a structural alteration affecting several contiguous genes spanning the putative MEN 2 region.

The peptides produced and secreted by pheochromocytoma may cause the coexistence of adrenal cortical abnormalities. Most of the patients had adrenal cortical hyperplasia with Cushing’s syndrome [13], some had hyperaldosteronism [26–29], some had concurrent adrenal cortical adenoma [13, 30–32]. Hyperaldosteronism in patients with pheochromocytoma can be categorized as secondary or primary aldosteronism [26]. Gordon [27] suggested that the simultaneous presence of pheochromocytoma and primary aldosteronism is probably a chance occurrence. The coexistence of the two conditions may also be caused by a genetic predisposition to endocrine dysplasia, or an interaction between the contiguous medullary and cortical tissues.

In this case, adrenal cortical lesion was found incidentally in an attempt to treat pheochromocytoma. In a summary of 208 patients with incidentally discovered adrenal masses, Kasperlik-
Zeluska et al. [33] reported that adrenal incidentalomas are fairly common, the adrenal lesion may be bilateral or unilateral, and the size of the adrenal masses range between 0.8 and 21 cm. Epidemiological data from Italy [34] showed that the majority of patients with adrenal incidentalomas were in the 5th and 6th decades and females were predominantly affected. Most of the adrenal incidentaloma were non-hypersecretory masses, only 7 out of 786 (0.89%) of the masses were aldosteronomas [35]. Kobayashi et al. [36] reported 12 cortical adenomas and 2 cortical nodular hyperplasia among 23 adrenal incidentalomas, and all the patients had normal peripheral levels of plasma cortisol and aldosterone. Corsello et al. [37] reported 2 out of 17 patients with adrenal incidentaloma had a high aldosterone serum concentration, their adrenal lesions proved to be dexamethasone-suppressible hyperaldosteronism with bilateral nodular hyperplasia and Conn’s adenoma respectively. In 32 patients with preoperative diagnosis of aldosterone-secreting adrenal cortical neoplasms, 10 of 32 (31%) had nodular hyperplasia and 1 of 32 (3%) had diffuse hyperplasia [38]. It is unfortunate that a complete dynamic endocrine study was not performed in our patient before the left adrenalectomy. The absence of spironolactone bodies has no diagnostic significance in determining the aldosterone producibility of the adrenal cortical nodules, because the patient did not receive spironolactone before surgery. Without initial serum ACTH, PRA and data on dexamethasone suppressibility, we can only infer, but not prove, that some adrenal cortical nodules might have aldosterone secretion, because the initial high serum aldosterone declined after left adrenalectomy.

It is often stated that 10% of catecholamine-producing chromaffin cell tumors are extraadrenal. In locating pheochromocytoma, CT scan usually reveals 95% of intraadrenal tumors [39], but it is less reliable when the tumor is extraadrenal or malignant [40]. [131I]-MIBG scintigraphy can screen the whole body with high specificity and locate extraadrenal sites or metastases of pheochromocytoma with better accuracy than CT [40]. During our patient’s first admission, the clinical symptom of labile blood pressure, the high urine VMA and the oval lesion in the left adrenal gland shown by CT scan led us to the impression of left adrenal pheochromocytoma. The lesion in the adrenal gland was proved to be cortical nodular hyperplasia. This experience reminds us of the importance of using [131I]-MIBG scintigraphy to search for potential extraadrenal lesions.

References


