Bilateral Pheochromocytoma Associated with Papillary Adenocarcinoma of the Thyroid Gland; Report of an Unusual Case

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Abstract

A 31-year old woman was admitted to our clinic complaining of high blood pressure, dizziness, constipation, mental irritability and weight loss. The physical examination revealed goiter in her neck. The plasma levels of norepinephrine and epinephrine were 3.45 and 0.76 ng/ml, respectively. Urinary excretion of norepinephrine was 1 mg and epinephrine was 32.2 µg/24-hours. The examination by radiography and radioactive isotope revealed a tumor in the left adrenal region and another in the left lower lobe of the thyroid. After the operations, pheochromocytoma and papillary adenocarcinoma of the thyroid gland were recognized pathologically. However, 17 months later, the recurrence of pheochromocytoma in the contralateral adrenal region was discovered and removed.

Although the co-existence of bilateral pheochromocytoma and papillary adenocarcinoma of the thyroid gland is not one of multiple endocrine neoplasia, to the best of our knowledge, only 7 such cases have been reported in the published literature.

Sipple's syndrome has been generally known as multiple endocrine neoplasia (MEN) type 2. In Sipple's original paper (1961), adenocarcinoma of the thyroid gland was postulated to associate with pheochromocytoma, though it is now generally accepted that this syndrome includes pheochromocytoma, medullary carcinoma of the thyroid gland and parathyroid adenoma. Subsequent to the publication of this report, some cases of pheochromocytoma accompanied with adenocarcinoma of the thyroid gland had been documented (Sahay, 1962; O'Brien, 1963; Kaye and Zak, 1964), until Williams (1965) pointed out that the association between pheochromocytoma and carcinoma of the thyroid gland was specifically with medullary carcinoma of the thyroid gland.

Although the association of pheochromocytoma and medullary carcinoma of the thyroid gland has been well documented thereafter, descriptions dealing with associated adenocarcinoma of the thyroid gland are rare and the interrelationship between pheochromocytoma and adenocarcinoma of the thyroid gland has remained unknown.

We present here a case, who had bilateral
pheochromocytoma and papillary adenocarcinoma of the thyroid gland, for the purpose of commenting on the relationship between both lesions.

Case Report

A 31-year-old woman was first admitted to our clinic in January, 1980. She had been quite healthy until November, 1978, when she began to feel palpitation and chest pain on ascending stairs. She also noticed dizziness and her blood pressure rose to 170/120 mmHg. Subsequently, constipation, mental irritability and a body weight loss of 5 kg occurred several months prior to admission.

On admission, she was found to be normally developed and her skin was dry. Her blood pressure was 180/130 mmHg. There was a small goiter in her neck, but other physical findings showed no abnormalities.

Routine determinations of peripheral blood cell count, chemistry, serology and urinalysis yielded negative or normal results except for a positive reaction for VMA in urine. The value of carcinoembryonic antigen (CEA) was 2.3 ng/ml (normal value, less than 5.0). Endocrinological examinations of plasma disclosed norepinephrine of 3450 pg/ml (177.5 ± 16.0), epinephrine of 760 pg/ml (37.0 ± 6.0), triiodothyronine of 1.26 ng/ml (0.6–1.9), thyroxine of 7.9 μg/dl (4.9–11.7), TSH of 1.76 μU/ml (less than 5.3) and calcitonin of 51.0 pg/ml (less than 165). 24-hour-urine contained norepinephrine of 1 mg (less than 0.05), epinephrine of 32.2 μg (less than 10), metanephrine of 0.13 mg (less than 0.3) and normetanephrine of 2.79 mg (less than 0.3). The diastolic pressure was decreased from 115 to 80 mmHg by intravenous infusion of phentolamine. Adrenal scintigram and selective phlebogram demonstrated a tumor measuring about 3 cm. in diameter in the left adrenal region. However, no tumor mass was found in the contralateral region. A blood sample drawn from the left adrenal vein contained about 8-fold higher concentrations of catecholamines than that from the right. It, therefore, seemed clear from these examinations that patient had a left adrenal pheochromocytoma. A decrease in uptake of radioactive iodine at left lower lobe, which coincided with the site of the nodule palpated, was observed in the thyroid gland scintigram, but the results of negative response to provocative test by calcium infusion, in addition to a normal plasma level of CEA, helped to rule out the possibility of medullary carcinoma of the thyroid gland. In March, 1980, she underwent left adrenalectomy. At that time, no mass was felt in the right adrenal gland and blood pressure was not increased by applying some pressure on this organ. The following month, left hemithyroidectomy, combined with cervical lymphadenectomies, was performed.

As shown in Fig. 1, the tumor was brown in color and measured 2.5 × 2.5 × 1 cm, weighing 6.0 g. The cut surface revealed

Fig. 1. The cut surface of the resected left adrenal gland. The tumor is well defined and encapsulated and the cut surface is dark gray without bleeding. Multi-focal cysts containing dark red fluid are present.
multi-focal cysts between homogeous brown-colored parenchyma, and they were filled with dark red fluid. Microscopically, the tumor cells varied considerably in size and shape and had granular abundant cytoplasm. Vascular-rich stroma was apparent (Fig. 2). The removed thyroid gland showed a well-defined neoplasm, $1.2 \times 0.7 \times 0.7$ cm, in size, weighing 1.0 g, at the middle part of the left lobe. Microscopic examination revealed well-differentiated papillary adenocarcinoma. The lining epithelium was composed of cuboidal cells with ovoid nuclei. They infiltrated the stroma. Psammoma bodies were present. There were no typical solid nodular patterns to indicate medullary carcinoma (Fig. 3).

As shown in Fig. 4, plasma concentrations of catecholamines, which had been normalized immediately after the adrenalectomy, increased gradually for several months up to twice as much as normal values. Blood pressure which had once decreased also began to rise. Moreover, a tumor-like shadow in the right adrenal region was noted by computed tomography of abdomen taken 12 months after the operation. In August, 1981, the patient was re-admitted because of severe abdominal pain. When the patient underwent laparotomy and an adhesive ileus was discovered, two tumors of about 1 cm. in diameter and transient increase in blood pressure were noticed on palpation of the right adrenal gland. These signs suggested strongly that the patient had an additional pheochromocytoma in the right adrenal gland, so right adrenalectomy was carried out. The resected tumor, weighing 1.0 g, was found to be a pheochromocytoma when examined pathologically.

![Fig. 2. Microscopical features of the left adrenal gland tumor. A large cellular neoplasm is shown in the medulla. The cells are rather fibrillar and anisocytotic in cytoplasm. The nuclei are oval in shape throughout the entire area, but occasionally are giant in size. Hematoxylin and eosin, x100.](image-url)
Fig. 3. Microscopical features of the thyroid tumor. The sheets of tumor cells constitute well-differentiated papillary adenocarcinoma, containing small tubular gland-like structure. Colloid is present. Hematoxylin and eosin, ×100.

Fig. 4. Arterial pressure and catecholamines excretion in urine after the first admission. Scatter-area surrounded by lines shows arterial pressure. abscissa: date, ordinate: arterial pressure and catecholamine excretion. Open columns show total amount of epinephrine in the 24-hour urine. Hatched columns show norepinephrine in a same manner to epinephrine. Open arrows indicate each surgical procedure. NE: norepinephrine. E: epinephrine.
After the last operation, during the follow-up period of about 3 years, she has remained asymptomatic and no recurrence was noticed.

The patient’s family history was as follows. Her mother and siblings were living and well but her aunt had hypertension. As her father is missing, the history of paternal relatives is unknown.

Discussion

So far as we know, there have been seven reported cases of adenocarcinoma of the thyroid gland associated with bilateral pheochromocytoma in the world, and after 1959, in which the existence of medullary carcinoma of the thyroid gland had been emphasized by Hazard et al., three such cases were reported (Sipple, 1961; Sahay, 1962; Ruppert et al., 1966).

Generally patients with bilateral pheochromocytoma are more likely to have a genetic basis for their disease and to have associated medullary carcinoma of the thyroid gland than those with unilateral pheochromocytoma. Our patient also had bilateral pheochromocytoma, but since the patient’s father is missing, it has not been possible to determine exactly whether our case was sporadic or hereditary. Nevertheless, it can be confirmed in view of histological findings, results of blood sample and lack of response to provocative test by calcium infusion that our case has not had medullary carcinoma in the thyroid gland.

The relationship of pheochromocytoma and adenocarcinoma of the thyroid gland in our case is unknown. No definite statements have been made with regard to the connection between them at present, but once adenocarcinoma of the thyroid gland had been thought to be one of MEN. Steiner et al. (1968) had tried to postulate the association of parathyroid tumors and papillary adenocarcinoma of the thyroid gland as MEN type 3. Ellenberg et al. (1962) had remarked that seven cases in a series of 93 cases of parathyroid adenoma had adenocarcinoma of the thyroid gland and this association was thought to be sufficiently well established. They had also speculated that hypercalcemia caused by parathyroid adenoma played a goitrogen capable of stimulating the thyroid to develop thyroid carcinoma. The present case produced no evidence of an exaggerated value of calcium or PTH, so it is unlikely for her to have parathyroid adenoma.

Sipple (1961) reported an increased incidence of carcinoma of the thyroid in patients with pheochromocytoma and noted that this association was 14 times greater than in the general population, considering that a fluctuating level in TSH secretion caused by circulating catecholamines stimulated thyroid tissue intermittently and thereby might be responsible for hyperplastic and neoplastic change in the thyroid gland. There were some results that supported this theory directly and indirectly (Zimmerman et al., 1954; Morris, 1955; Soderberg, 1958; Ackerman and Arons, 1958). Recently heightened exposure to the amines produced by the tumor has been felt to play a role in the development of further endocrine abnormalities (Baggott, 1983).

Papillary adenocarcinoma of the thyroid gland is usually more likely to occur in females than in males and often exists quietly. In Japan, a few cases of associated adenocarcinoma of the thyroid gland with unilateral pheochromocytoma were reported (Saito et al., 1974; Sada et al., 1978; Kikuchi et al., 1982) and all of them were noticed in females. Therefore, it is proper to conclude that each tumor in this case developed casually, but as far as we know our case is the first one in Japan reported to be a combination of bilaterally developed pheochromocytoma and papillary adenocarcinoma of the thyroid. We believe that in future a case of pheochromocytoma
attended with atypical endocrine tumors like this case will be worthy of note.

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References


