Cushing’s Disease Associated with Adrenal Myelolipoma, Adrenal Calcification and Thyroid Cancer

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Abstract. A 51-year-old woman with Cushing’s disease associated with adrenal myelolipoma is reported. A further characteristic feature was the coexistence of bilateral adrenal calcification and thyroid cancer. Previously several cases of adrenal myelolipoma associated with endocrine dysfunction were reported. The combination of Cushing’s disease and adrenal myelolipoma has only been described in two cases of recurrent Cushing’s disease but never in an initial occurrence of Cushing’s disease. Continued stimulation by excessive adrenocorticotropic hormone (ACTH) not only developed adrenal hyperplasia but also might be involved in the pathogenesis of adrenal myelolipoma.

Key words: Cushing’s disease, Adrenal myelolipoma, Adrenal calcification, Thyroid cancer.

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ADRENAL myelolipoma, being a non-functioning benign tumor consisting of admixtures of fat cells and hematopoietic tissue, is usually discovered accidentally at autopsy because this disease usually progresses asymptptomatically. However, cases diagnosed during the lifetime of the patient have increased because of the recent advance in imaging diagnosis. On the other hand, participation of the adrenocorticotropic hormone (ACTH) or cortisol has received attention as its cause, because some cases associated with dysfunction of the pituitary-adrenal axis have been reported.

In this article, we report a case of Cushing’s disease associated with adrenal myelolipoma, adrenal calcification and thyroid cancer.

Case Report

In February, 1991, a 51-year-old female was admitted to our hospital with Cushing’s syndrome. Hypertension was pointed out in a medical check in autumn, 1990. On admission, she was 154 cm tall and weighed 61 kg. Her blood pressure was 130/90 mmHg. Cushingoid signs such as moon face, central obesity, acne and hirsutism were observed. A little finger tip sized node was palpable in the left lobe of the thyroid gland. Routine examinations including urinalysis, peripheral blood, biochemistry and electrolytes were within the normal range. Neurological and ophthalmological examinations were normal.

Endocrinological examination

The blood cortisol value was increased, with the disappearance of circadian rhythm (0800 h, 17.4 µg/dl; 2000 h, 10.1 µg/dl). Overnight dexamethasone
suppression test elicited no suppression of cortisol (0800 h, 19.3 µg/dl). The fasting basal ACTH level was 43.8 pg/ml and its responsiveness to CRH (100 µg; Peptide Institute, Osaka) was exaggerated (peak: 210.0 pg/ml). (ACTH was measured with an IRMA kit.). The basal 24-h urine 17-OHCS was increased (8.7–11.6 mg/day) and it was completely suppressed by 8 mg dexamethasone administration (1.4 mg/day). Metyrapone administration doubled the urine 17-OHCS (20.2 mg/day). Selective venous sampling, by means of catheterization of the inferior petrosal sinus, revealed that the blood level of ACTH on the left side was twice as high as on the right side. The thyroid function was normal. A 75 g oral glucose tolerance test (OGTT) showed a borderline pattern (fasting; 102, 2-h; 138 mg/dl).

**Radiological examination**

Computed tomography (CT) of the abdomen: Right adrenal gland: Slight swelling and a spotted calcification were found in the internal region (Fig. 1a). Left adrenal gland: A 3×2 cm mass lesion was found, and its edge was slightly uneven. Fine spotted calcifications were observed in the upper region of the mass. (Fig. 1b). A round low dense area was found in the lower region of the mass (Fig. 1c).

CT of the head revealed a low dense area on the left side of the pituitary gland, and a further low dense area 4 mm in diameter in its central region after administration of contrast medium (Fig. 2). Magnetic resonance imaging (MRI) on the head showed that the circumference of the low intensity lesion on the left side of the pituitary gland was slightly enhanced after Gd-DTPA.

CT of the neck revealed an irregular low dense area 1 cm in diameter in the left lobe of the thyroid gland, and a low absorption area 7 mm in diameter also in the isthmus. The class V was diagnosed by aspiration biopsy cytology under echographic examination.

An I-131 adosterol scintigram revealed enhanced calcification were found in the internal region (Fig. 1a). Left adrenal gland: A 3×2 cm mass lesion was found, and its edge was slightly uneven. Fine spotted calcifications were observed in the upper region of the mass. (Fig. 1b). A round low dense area was found in the lower region of the mass (Fig. 1c).

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An I-131 adosterol scintigram revealed enhanced
uptake in both adrenal glands.

The patient was diagnosed as having an ACTH secreting pituitary adenoma, left adrenal mass, bilateral adrenal calcifications and thyroid carcinoma. Malignancy of the left adrenal mass could not be ruled out.

In May, 1991, total thyroidectomy, left adrenalectomy and biopsy of the right adrenal gland were carried out. In September, 1991, the pituitary tumor was extirpated by a transsphenoidal route.

**Histopathology**

**Adrenal gland:** The left adrenal gland was extirpated and found to be 15 × 25 × 50 mm and 11 g and to have many nodules with a maximum diameter less than 8 mm on its cut surface (Fig. 3). Jelly-shaped contents 10 mm in diameter were found in the lower region which corresponded to the low dense area detected by CT. Histologically, the hyperplasia of the cortex, and nodular lesions due to compact-type cells, intermediate-type cells and clear-type cells were found here and there (Fig. 4). Moreover, small calcification foci were found scattered in the cortex. An adrenal myelolipoma was diagnosed because the jelly-shaped lesion consisted of hematopoietic cells with 3 cell lines and fatty tissue (Fig. 5). Biopsy of the right adrenal cortical section revealed hyperplasia and a nodular lesion in the adrenal cortex.

**Pituitary adenoma:** Chromophobe adenoma were composed mainly of cells characterized by scant cytoplasm (Fig. 6). Only anti-ACTH antibody was positively stained by immunohistochemistry.

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**Discussion**

The concept of adrenal myelolipoma was clarified by Gierke [1] in 1905, and the first case extirpated surgically was reported by Dyckman and Freedman [2] in 1957. It is known that this tumor is endocrinologically non-functional. As to the etiology of this disease, various theories such as the presence of bone marrow rest during embryonic life and establishment of viable areas of bone marrow and metaplasia of the adrenal tissue had been proposed, but the latter theory has been mainly considered in recent years. Selye and Stone [3] reported in 1950 that myelolipoma-like change in the adrenal cortex occurred following the administration of crude anterior pituitary extracts and testosterone in rats. Moreover, Olsson et al. [4] reported in 1973 that metaplasia of the adrenal tissues might be induced by development of necrotic tissues in patients who were subject to chronic ailments such as malignant diseases and cardiovascu-
lar diseases. In 1958, Plaut [5] suggested a somewhat causal relationship because endocrinological complications were found in 9 of 100 autopsied cases with myelolipoma.

In recent years, Bennett et al. [6] carried out subtotal adrenalectomy in Cushing’s disease, and reported recurrent cases of Cushing’s disease complicated with adrenal myelolipoma after 13 years. They reported that stimulation of the adrenocorticotropic hormone (ACTH) or cortisol may be related to the pathology because adrenal myelolipoma clinically occurs often in cases with hypercortisolism.

Our case is similar to the case reported by Bennett et al. [6], but pituitary lesion was not histologically studied in their case and complication of the adrenal myelolipoma was not found at the initial subtotal adrenalectomy. It is considered that

Fig. 4. Microscopical findings show adrenocortical nodular hyperplasia (HE stain, original magnification ×13).

Fig. 5. Pathological specimen shows diffuse fat tissue with myeloid elements. The border of the myelolipoma is well defined (HE stain, original magnification ×33).
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this is the first reported case in which both ACTH-secreting pituitary adenoma and adrenal myelolipoma were extirpated. As cases in which excessive ACTH is considered to cause the adrenal myelolipoma, cases with Nelson's syndrome [7] or congenital adrenal hyperplasia [8, 9] have been already reported. As cases in which hypercortisolism is considered to cause the adrenal myelolipoma, cases [10, 11] with Cushing's syndrome or Kanj et al's case [12] have also been reported.

On the other hand, calcified lesion was found in the bilateral adrenal glands in this case. It is well known that calcified lesion is complicated with myelolipoma and Biresi [13] reported in 1954 that calcified lesion was found in 10 of 54 cases, and Sasano [14] also suggested in 1964 that calcification was rare, but occasionally occurred. Subsequently, Behan et al. [15] reported that complication of adrenal calcifications was found in 3 of 14 cases in roentgenographical study of the adrenal myelolipoma, and that calcified lesions were found in the bilateral adrenal glands in their cases, but adrenal myelolipoma was only found in the unilateral adrenal gland. In this case also, calcification foci were clearly found in the bilateral adrenal glands, whereas imaging findings did not show complication with myelolipoma in the right adrenal gland.

Furthermore, papillary cancer in the thyroid gland was also a complication in this case. It is well known that multiple endocrine neoplasia type I (MEN-I) is a disease developing tumor or hyperplasia in the pituitary, parathyroid and pancreas. It also frequently complicates adrenal cortical lesion or thyroid lesion [16]. Banik et al. [17] reported an unusual case of MEN-I complicated with papillary cancer in the thyroid gland, adrenal cortical cancer and adrenal myelolipoma. It was considered that complication of the thyroid lesion developed accidentally in our case because abnormality of the pancreas has not been observed until now and no parathyroid lesion was found at total thyroidectomy.

References


