NOTE

A Case of ACTH-Independent Bilateral Macronodular Adrenal Hyperplasia Successfully Treated by Subtotal Resection of the Adrenal Glands: Four-Year Follow-Up

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Abstract. We report ACTH-independent bilateral macronodular adrenal hyperplasia (AIMAH) seen in a 48-year-old male with a history of rectal and skin cancer. Bilateral multiple adrenal nodular lesions on abdominal CT scans, elevated early morning plasma cortisol levels with undetectable plasma ACTH, increased 24-hour urinary free cortisol excretion, and loss of the normal circadian rhythm in cortisol secretion established the diagnosis of AIMAH. Subtotal resection of the adrenal glands preserving lower one third of the left side was performed, considering the unfavorable effects of total adrenalectomy on future treatment of his malignancies. He has been doing well for four years with normal plasma ACTH and cortisol levels. This case suggests that subtotal resection of the adrenal glands may be applicable to selected patients.

Key words: Adrenal gland, Macronodular hyperplasia, ACTH-independent, Subtotal resection
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ACTH-INDEPENDENT macronodular adrenal hyperplasia (AIMAH) is a distinctive subtype of Cushing's syndrome, and bilateral adrenalectomy is thought to be necessary to cure the hypercortisolemia. We report here an unusual case of AIMAH in which cortisol hypersecretion has been well controlled for four years after subtotal resection of the adrenal glands.

Case report

The patient is a 47 year-old male. While under-

going treatment for facial skin cancer (squamous cell carcinoma), he was found to have hypertension and hyperglycemia. Abdominal CT scans showed enlargement of bilateral adrenal glands. He had undergone Miles's operation for rectal cancer 6 years before his first visit. Neither of the above described cancers was hormone-producing.

He was 171 cm tall and weighed 60 kg. Blood pressure was 170/110 mmHg at rest. His skin was atrophic and subcutaneous blood vessels were observed. Bruisability with ecchymoses was noted. There was no central obesity or buffalo hump. Except for elevated fasting plasma glucose level (201 mg/dl), his blood chemistry and complete blood count were within normal limits. HbA1c was elevated at 9.1%. Diabetic glucose tolerance curve was present.

Early morning plasma cortisol levels were elevated beyond normal range (22.3 µg/dl, NR: 4–18.3).

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Twenty four-hour urinary free cortisol excretion was high (208 $\mu\text{g/day}$, NR: 4–18.3). Normal circadian rhythm in cortisol secretion was lost (8': 22.3 $\mu\text{g/dl}$, 16': 20.4 $\mu\text{g/dl}$, 22': 19.2 $\mu\text{g/dl}$). There was no suppression of cortisol secretion by administration of low- and high-dose overnight dexamethasone suppression test (2 mg: 17.3 $\mu\text{g/dl}$, 8 mg: 16.6 $\mu\text{g/dl}$). Plasma ACTH, urinary 17-OHCS, and urinary 17-KS were not affected by administration of metopirone. Plasma ACTH was undetectable (<5 pg/ml) in the basal state and after metyrapone or CRH. Reaction to stimulation tests (CRH, 100 μg iv, GRH 100 μg iv, TRH 500 μg iv, LH-RH 100 μg iv) was decreased in ACTH (pg/ml) ($<5 \rightarrow <5$), Cortisol ($\mu\text{g/dl}$) (14.4 $\rightarrow$ 15.6), TSH ($\mu\text{U/ml}$) (0.5 $\rightarrow$ 3.8), and FSH (mIU/ml) (14 $\rightarrow$ 17), whereas normal in LH, GH, and PRL.

Abdominal ultrasonography, CT scans (Fig. 1-A)

and MRI showed bilaterally enlarged adrenal glands with multiple nodules, which showed low signal intensity on T1-weighted images and slightly high signal intensity on T2-weighted images as has been reported [1]. Images of the nodules were enhanced by gadolinium administration. Increased uptake of radioisotopes was noted on adrenal scintigram with ^{131}I -adosterol (Fig. 1-B). Empty sella was found on cranial MRI in this case.

Right adrenalectomy and resection of the upper two-third of the left adrenal gland were performed on June 9, 1997. The resected adrenal glands weighed 35 g (right) and 50 g (left), and contained multiple macroscopic nodules (Fig. 1-C). Pathologically, the nodules, which consisted mainly of clear cells arranged in acini and cords, compressed the surrounding cortex.

Immunohistochemical study demonstrated immu-

Fig. 1. (A): An abdominal CT scan. Adrenal glands were enlarged with multiple nodules. (B): Adrenal scintigram. Increased uptake of radioisotopes was noted. (C): The resected adrenal glands consisted of multiple yellowish nodules. (D) and (E): Immunohistochemical study demonstrated immunoreactivity of P-450_{17 α} in small compact cells (E) and 3 β -HSD in large clear cells (D).

noreactivity of P-450_{17α} in small compact cells and 3β-hydroxysteroid dehydrogenase (3β-HSD) in large clear cells (Fig. 1-D, E). Results are consistent with the reported feature of AIMAH [2–5].

After operation, basal secretion of cortisol returned to normal levels (8.7 μg/dl). Urinary free cortisol returned to normal range (40 μg/day). Positive reactions to rapid ACTH test were resumed. Diurnal variation of plasma ACTH and cortisol was restored. Plasma cortisol was suppressed by administration of dexamethasone. He has been doing well for four years with normal plasma ACTH (9 pg/ml, NR: 9–52) and cortisol (13.6 μg/dl) levels.

Serum or plasma hormonal values were determined by radioimmunoassay or colorimetric assay with kits or reagents described below: Allegro ACTH kit (Japan Medipysics) for plasma ACTH; gamma-coat cortisol kit (Baxter) for plasma and urinary cortisol; Spac LH kit (Dai-ichi RI) for serum LH; Spac FSH kit (Dai-ichi RI) for serum FSH; TSH RIA beads (Dynabott) for serum TSH; GH kit Daiichi (Dai-ichi RI) for serum GH; Spac PRL kit (Dai-ichi RI) for serum PRL; AVP IA kit (Mitsubishi Kagaku) for plasma ADH.

Discussion

In the current case, we performed subtotal resec-

tion of the adrenal glands, considering the unfavorable effects of total adrenalectomy on patient's general condition and future management of cancers. The patient is at high risk of developing recurrent tumors, and cortisol supplement might be difficult when chemotherapy or other extensive therapy is necessary. We preserved the lower one-third of the left adrenal gland which we think is the easiest part for removal when the control of cortisol hypersecretion has failed and resection of the remaining adrenal gland is necessary. In addition, the intact left adrenal vein is favorable for efficient secretion of the adrenal steroids. He has been doing well for four years without evidence of cortisol hypersecretion. Basal levels of plasma ACTH and plasma cortisol have remained normal without any symptoms of adrenal insufficiency. Bilateral adrenalectomy is believed to be necessary to cure the hypercortisolemia in AIMAH cases [6] and there has not been any report on preservation of the adrenal gland. Our case, however, suggests that subtotal resection of adrenal glands may be a choice for selected patients. There has been a report suggesting that cortisol production in AIMAH is inefficient, and that the cause of Cushing's syndrome may be related to the marked increase in the number of cells or to the bulk of the tumor [7]. In this regard, mass reductive surgery may produce favorable control of cortisol secretion in AIMAH cases for a considerable period.

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