Black Adrenal Adenoma Causing Preclinical Cushing's Syndrome

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(Received June 24, 2009; Accepted March 9, 2010)

Functioning black adrenal adenoma (BAA) rarely causes preclinical Cushing's syndrome (CS). In the present case, a 46-year-old Japanese Peruvian woman presented with left flank pain and hypertension. Abdominal computed tomography showed that she had a 15-mm in diameter, round, left adrenal adenoma. She had no physical features of CS, such as moon face, buffalo hump, truncal obesity, or purple striae. Endocrinological examination showed that the plasma adrenocorticotropic hormone (ACTH) level was below the detectable level, despite a serum cortisol level within the normal range. A normal cortisol circadian rhythm was not present. Dexamethasone (1 mg and 8 mg) suppression testing did not decrease serum cortisol levels to the reference levels. These findings were compatible with preclinical CS. The left adrenal adenoma was laparoscopically removed. Examination of the surgical specimen revealed unilateral double adrenal adenomas of the left adrenal gland, one of which was a BAA. The BAA measured 20 × 11 × 10 mm. Microscopically, the BAA showed proliferation of compact cells containing numerous brown-pigmented granules. There were also foci of myelolipomatous degenerative changes in the tumor. The compact cell zones remained in the adrenal cortex adjacent to the BAA showed atrophic change. These findings indicated that BAA appeared to have caused preclinical CS in this patient.

Key words: Black adrenal adenoma, preclinical Cushing's syndrome, unilateral double adrenal adenomas

INTRODUCTION

Adrenal adenoma with a black or brown appearance is known as a black adrenal adenoma (BAA). BAA is predominantly composed of compact cells containing numerous pigmented granules [1]. Although non-functioning BAA is reported to be seen about 10% at autopsy [2], BAA with full-blown Cushing's syndrome (CS) is quite rare [3].

Preclinical CS is defined as autonomous glucocorticoid production without specific signs and symptoms of CS. The diagnosis of preclinical CS is based on the criteria of two or more abnormal results on classical tests of the hypothalamic-pituitary-adrenal axis without typical physical findings of CS, such as moon face, buffalo hump, truncal obesity, or purple striae [4, 5]. While preclinical CS is found in approximately 6% of patients with adrenocortical incidentaloma [6], preclinical CS caused by BAA is rare. There are only five cases reported in the English literature [7–11]. Here, we describe a case of BAA causing preclinical CS.

CASE REPORT

A 46-year-old Japanese Peruvian woman was referred to our hospital with left flank pain and hypertension. She had a two-year medical history of hypertension without any medication. Her height was 146 cm and her body weight was 61 kg. Her blood pressure was 156/90 mmHg and her heart rate was 66 beats/min and regular. Mild left flank tenderness was present. The patient had no overt physical features of CS, such as moon face, buffalo hump, truncal obesity, or purple striae.

Laboratory data are summarized in Table 1. Complete blood cell counts were within the normal range. Blood chemistry showed elevated levels of alanine aminotransferase and total cholesterol. Results of endocrinological examinations are shown from Table 2-1 to 2-3. In summary, the plasma adrenocorticotropic hormone (ACTH) level was suppressed to less than the detectable level, but levels of other hormones were within normal range. Normal circadian rhythm of serum cortisol was not observed. Low-dose (1 mg) and high dose (8 mg) dexamethasone suppression tests (DST) did not suppress serum cortisol level to reference ranges.

An abdominal computed tomography (CT) scan was performed to investigate the flank pain, and a 15-mm in diameter, round tumor in the left adrenal gland was observed (Fig. 1). Adrenal scintigraphy with ^{131}I-adsterol showed significant accumulation in the left adrenal gland, compared with the right adrenal gland (Fig. 2).

Laparoscopic left adrenalectomy was performed. The patient's recovery was uneventful, and she was normotensive. Oral hydrocortisone, 20 mg/day, was given as replacement therapy. The replacement dose of hydrocortisone was gradually decreased and stopped six months after the surgery. The patient has been doing well for the last three years.

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Table 1

Complete blood cell counts	Value	Normal range
WBC (/μl)	7300	4000–8000
RBC ($\times 10^4$/μl)	459	380–480
Hemoglobin (g/dl)	13.7	11.5–15.5
Hematocrit (%)	41.7	34.0–42.0
MCV (fl)	90.9	84.0–99.0
MCH (pg)	29.8	27.0–32.0
MCHC (%)	32.8	32.0–36.0
Platelets ($\times 10^4$/μl)	22.4	14.0–40.0

Blood chemistry	Value	Normal range
Total protein (g/dl)	6.8	6.5–8.0
Creatinine kinase (IU/l)	92	30–140
AST (IU/l)	28	<30
ALT (IU/l)	36	<35
Creatinine (mg/dl)	0.5	0.5–0.8
Plasma glucose (mg/dl)	93	70–109
Total cholesterol (mg/dl)	264	140–220
Triglyceride (mg/dl)	57	50–150
Sodium (mEq/l)	141	136–145
Potassium (mEq/l)	3.8	3.5–4.8
Chloride (mEq/l)	106	98–108

WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2–1

Basal endocrinological evaluation	Value	Normal range
Plasma ACTH (pg/ml)	<5	7.4–55.7
Serum Cortisol (μg/dl)	7.3	4.0–18.3
Serume DHEAS (μg/dl)	47.7	19–231
Palsma renin activity (ng/ml/h)	0.4	0.3–5.4
Plasma Aldosterone (pg/ml)	70	30–159
Plasma Adrenaline (pg/ml)	8	<100
Plasma Noradrenaline (pg/ml)	214	100–450
Plasma Dopamine (pg/ml)	<5	<20
Urine cortisol (μg/day)	21.3	11.2–80.3
Urine 17-KS (mg/day)	3.2	2.4–11.0
Urine 17-OHCS (mg/day)	5.2	2.2–7.3
Urine aldosterone (μg/day)	7.7	<10

ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate; 17-KS, 17-ketosteroids; 17-OHCS, 17-hydrocorticosteroids.

Table 2–2 Circadian rhythm of serum cortisol

Clock time	6:00	16:00	0:00
Serum Cortisol (μg/dl)	6.8	8.3	8.4

Table 2–3 Dexamethasone suppression test

Dexamethasone dose	Serum Cortisol (μg/dl)	Reference range
1 mg	10.3	<5
8 mg	9.3	<50% of the base line

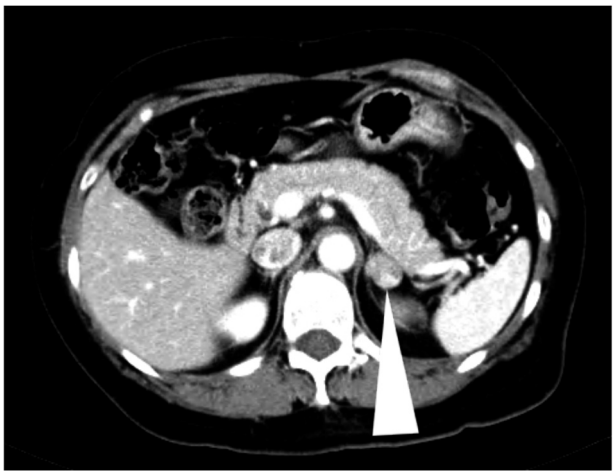

Fig. 1 Abdominal computed tomography shows a 15-mm, round, and well-circumscribed tumor in the left adrenal gland. The white arrow head indicates.

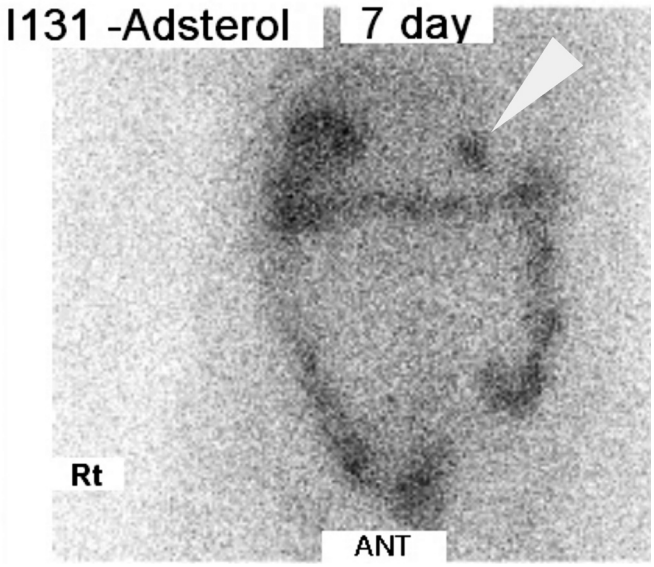

Fig. 2 Adrenal scintigraphy with ^{131}I-adsterol (anterior-posterior view) shows significant accumulation in the left adrenal gland. The white arrow head indicates.

PATHOLOGICAL FINDINGS

Macroscopic findings

The resected specimen showed double oval adrenal adenomas: one measured 20 × 11 × 10 mm (adenoma #1), and the other measured 6 × 5 × 5 mm (adenoma #2) (Fig. 3). Both adrenal adenomas were well circumscribed but not completely encapsulated. The cut surface of the large adrenal adenoma was brownish black. The cut surface of the small adrenocortical tumor was golden yellow.

Microscopic findings

Adenoma #1 (BAA): The tumor was considered to be an adrenal adenoma according to the criteria of Weiss [12]. The tumor cells of the large adenoma consisted mostly of compact cells, including focally lipid-containing cells. The compact cells were polygonal and arranged in sheets and cords. The nuclei were vesicular and mildly pleomorphic. The cytoplasm contained various-sized, brown-pigmented granules (Fig. 4–A). There were also foci of myelolipomatous degenerative changes in the tumor (Fig. 4–B). The adjacent non-tumorous adrenal cortex was decreased in thickness and consisted mainly of zona reticularis with prominent adrenal medulla. The compact cell zones remained partially in the adjacent atrophic adrenal cortex (Fig. 5).

Adenoma #2: This tumor was also considered to be an adrenal adenoma according to the criteria of Weiss [12]. The tumor was predominantly composed of clear cortical cells without brown-pigmented granules (Fig. 6).

DISCUSSION

Our patient showed no overt physical characteristics of CS. Endocrinological examinations revealed undetectable level of plasma ACTH with normal level of serum cortisol. The patient did not show the normal circadian rhythm of serum cortisol. DST failed to decrease the serum cortisol level to the reference level [13–15]. Significant accumulation of ^{131}I-adsterol was observed in the left adrenal gland. The patient's hypertension was ameliorated after the adrenalectomy, but hypertension is not a significant sign of preclinical CS [5]. This patient's findings were compatible with preclinical CS [4, 5].

There was a report that a case of full-blown CS due to BAA was not visualized by adrenal scintigraphy with ^{131}I-adsterol because the poor lipid content of compact cells of the reticularis zone in BAA might be responsible for the lower cholesterol uptake [16]. In the present patient, the cut surface appearance of the large adenoma was brownish black, suggesting that it was lipid-rich compared with the adenoma with a completely dark black appearance. It was speculated

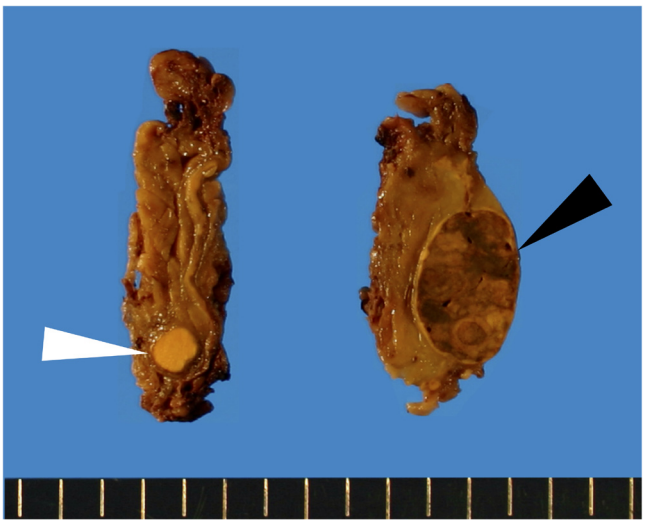

Fig. 3 The cut surface of the large adenoma (20 × 11 × 10 mm) is brownish black (adenoma #1). The black arrow head indicates. The cut surface of the small adenoma (6 × 5 × 5 mm) is golden yellow (adenoma #2). The white arrow head indicates.

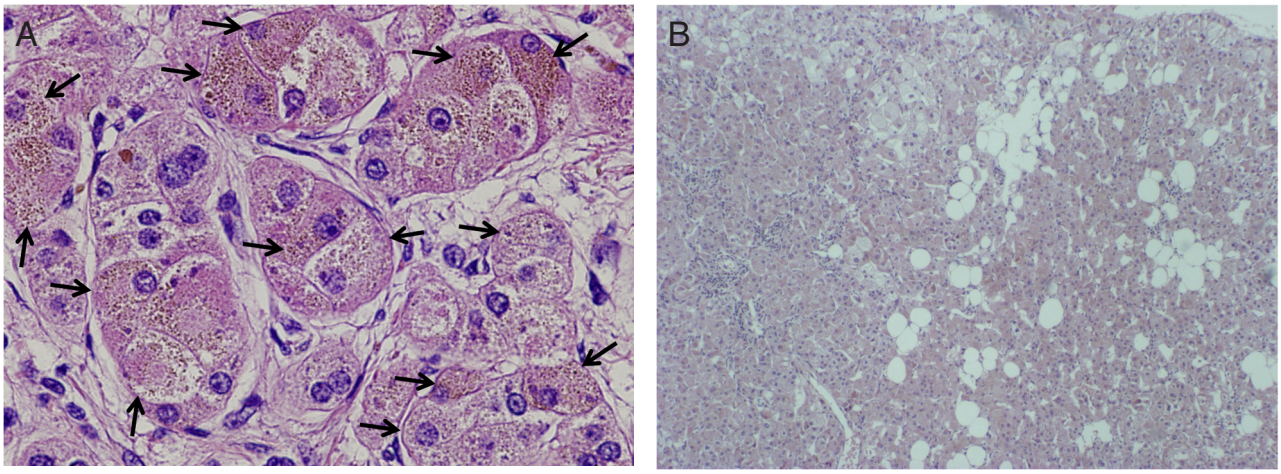

Fig. 4 (A) Adenoma #1 (black adrenal adenoma): The tumor cells of the large adenoma consist predominantly of compact cells, including focally lipid-containing cells. The compact cells are polygonal and arranged in sheets and cords. The nuclei are vesicular and mildly pleomorphic. The cytoplasm contains various-sized brown-pigmented granules. The arrows indicate brown-pigmented granules. Original magnification × 400.
(B) There were also foci of myelolipomatous degenerative changes in the tumor. Original magnification × 40.

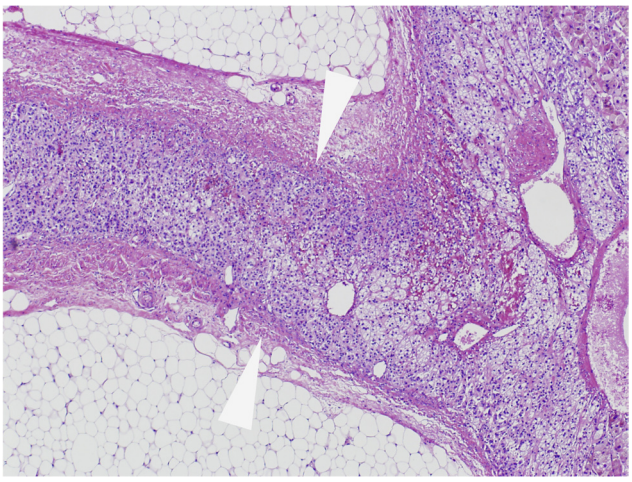

Fig. 5 The adjacent non-tumorous adrenal cortex is decreased in thickness and consists mainly of zona reticularis with prominent adrenal medulla. The compact cell zones remain partially in the adjacent atrophic adrenal cortex. The white arrow heads indicate. Original magnification × 40.

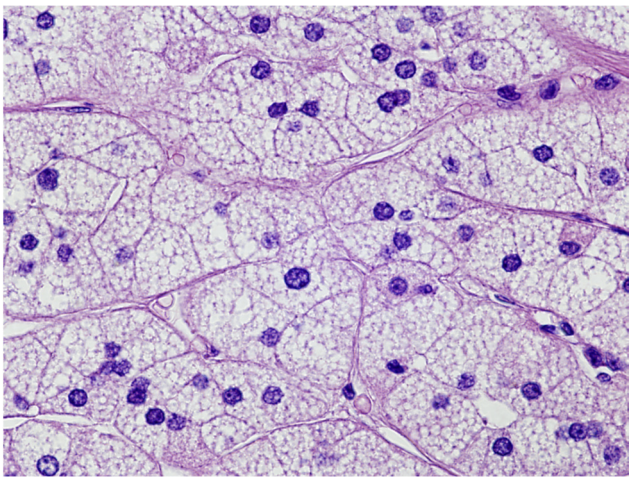

Fig. 6 Adenoma #2: The tumor is predominantly composed of clear cortical cells without brown-pigmented granules. Original magnification × 400.

that this patient's BAA was visualized by adrenal scintigraphy with ^{131}I-adsterol because it had more lipid-rich content absorbing cholesterol than the completely dark black adrenal adenoma.

BAA is classified into either a functional or a non-functional lesion according to its endocrine activity [3, 17]. Both types of lesion are macroscopically black or brown, and histological findings reveal a predominance of compact cells with few lipids. Ultrastructurally, the number of lysosomes, endoplasmic reticulum, mitochondria, and particularly the characteristic lipofuscin granules were found to be increased [1]. These pigmented granules, lipofuscin, give the adenoma its black gross appearance. Generally, lipofuscin accumulation in the cardiac muscle, hepatocyte, and brain nerve tissue can be seen as part of the aging process. The storage of lipofuscin is based on lipid peroxidation [18]. The lysosomes absorb the remaining intracellular products, including the product of lipid peroxidation. As a result of non-digestion by the lysosomes, lipofuscin is accumulated as a residual body. Suzuki *et al*. suggested that, based on the ultrastructure of lipofuscin, the origin of lipofuscin differs depending on whether the adenoma has endocrine activity [1]. They speculated that lipofuscin in BAA is of a lysosomal origin elaborated by longstanding cellular activity.

On pathology, the present patient had double adrenal adenomas. Some reports indicated that multiple adrenal adenomas including black adenoma caused preclinical CS. Okura *et al*. reported that magnetic resonance imaging study revealed three sequential tumors in the right adrenal gland and one of the three tumors was black adenoma producing cortisol [9]. Saito *et al*. indicated that two adrenal tumors were composed of a golden-yellow portion admixed with a brown portion, and the two adrenal tumors produced both cortisol and mineralcorticoid [10].

It was clinically important in the present case to determine whether the BAA or the other adenoma produced cortisol. It was suggested that functiocal BAA had some pathological features. Functional BAAs usually measure 20 to 30 mm in diameter [19]. In functional BAA, there are occasionally foci of lipomatous or myelolipomatous degenerative changes within the tumor and the attached adrenal remnant shows marked cortical atrophy [20]. In the present case, the BAA measured 20 × 11 × 10 mm, but the other adenoma measured 6 × 5 × 5 mm. There were also foci of myelolipomatous degenerative changes in the BAA. The compact cell zones remained in the adrenal cortex adjacent to the BAA showed atrophic change. It appeared that the large adenoma, the BAA, was functioning, and the small adenoma was non-functioning.

In conclusion, we have described a rare case of a woman with preclinical CS resulting from a cortisol-secreting BAA.

ACKNOWLEDGEMENTS

Authors thank Johbu Itoh, Ph. D., for his excellent technical assistance.

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