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Case Report

A Case of Adrenal Incidentaloma in which Autonomous Cortisol Production to become Clear during a Very Short Term

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Abstract A 57-year-old woman was admitted to the hospital for the further evaluation of a left adrenal incidentaloma measuring 45 mm x 33 mm. She had no signs of the clinical manifestation of hypercortisolism. An endocrine evaluation revealed that her ACTH level was normal and cortisol values were almost normal pattern excluding the value at 9 PM slightly rising, however, the cortisol was not completely suppressed by the overnight administration of 1 mg dexamethasone. These findings indicated that subtle abnormalities of the hypothalamo-pituitary-adrenal axis were present in this case. After 3 months, surprisingly, the ACTH was suppressed to low levels. Further hormonal investigations revealed that the cortisol level was normal but had an abnormal diurnal rhythm and was not suppressed completely by a 1 mg or an 8 mg overnight dexamethasone dose. Adrenal scintigraphy revealed positive uptake in the left adrenal tumor with no uptake in the right adrenal gland. The patient underwent a left laparoscopic adrenalectomy. Microscopically, the tumor displayed histopathological features in common with ACTH-independent macronodular adrenocortical hyperplasia, including clear cell predominance, a pattern of small compact nests in clear cell areas, and a cord-like arrangement of small compact cells. An in situ hybridization study demonstrated the hybridization signals for P-450scc, 3 β -HSD, P-450c21, P-45011 β , and P-45017 α which were observed in the clear cells as well as compact cells, the compact cells being more intensely stained. This case indicates the ability of autonomous cortisol production to become clear during a very short term and a more detailed and careful short-time follow-up should be recommended in patients with adrenal incidentalomas.

Introduction

Recently, the diagnosis of adrenal incidentalomas has been increasing due to the widespread use of diagnostic techniques such as ultrasonography, computer tomography (CT), and magnetic resonance imaging (MRI)¹⁾. Most of the cases of adrenal incidentaloma have been reported to be either nonfunctioning tumors or hormonally inactive adrenal tumors, but some cases have

been associated with autonomous cortisol secretion without specific signs and symptoms of Cushing's syndrome, which is termed preclinical Cushing's syndrome or subclinical Cushing's syndrome^{2)~5)}. Since long-term prospective studies assessing the outcome of the preclinical hypercortisolism are limited, the natural course of this disease remains unknown and concern exists as to the risk of progression from preclinical to overt Cushing's syndrome^{6)~8)}. Furthermore controversy still remains regarding the optimal follow-up strategy⁹⁾. We herein report an interesting case of adrenal incidentaloma in which autonomous cortisol production became definite during a very short term.

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Case Report

Clinical and Hormonal Findings (Fig. 1)

A 57-year-old female was referred to our hospital for further evaluation of a left adrenal tumor discovered by computed tomography (CT) performed for dyspepsia. On physical examination, she was 157 cm tall and weighed 59.7 kg. She did not have any Cushingoid features, such as a moon face, hirsutism, acne, buffalo hump, or abdominal striae. Her blood pressure was 120/64 mmHg. A routine laboratory examination showed a mild elevation of her liver enzymes (γ -glutamyl transferase : 71 U/L, alanine aminotransferase : 42 U/L), a total cholesterol level of 223 mg/dl, and a triglyceride level of 200mg/dl with no other abnormalities (Table 1). An endocrine evaluation revealed the plasma ACTH level to be normal (0900h 11.5 pg/ml) and cortisol levels were almost normal pattern except the value at 9 PM was slightly high. (0900h 17.3 μ g/dl, 1700h 12.2 μ g/dl, 2100h 6.1 μ g/dl) ; however the plasma cortisol was not completely suppressed by the overnight administration of 1 mg dexamethasone (4.0 μ g/dl). The urinary excretion of free cortisol (21.8 μ g/day), urinary 17-hydroxycorticosteroid (17-OHCS : 2.1mg/day), and 17-ketosteroid (17-KS : 7.1 mg/day) was unremarkable. The other endocrinologic data were as follows : Plasma aldosterone, 62.7 pg/ml ; plasma renin activity (PRA), 0.8 ng/ml/hr ; plasma epinephrine, < 5 pg/ml ; plasma norepinephrine, 90 pg/ml ; plasma dopamine, < 5 pg/ml ; urinary epinephrine, 6.8 μ g/day ; urinary norepinephrine, 80.9 μ g/day ; urinary metanephrine, 0.04 mg/day ; urinary normetanephrine, 0.19 mg/day ; urinary vanillylmandelic acid, 2.8 mg/day ; and urinary homovanillic acid, 3.0 mg/day. An abdominal CT scan revealed a nodular mass in the left adrenal gland measuring 45 mm \times 33 mm in size, which was hypodense, homogenous, with well-defined margins and rapid enhancement after i.v. contrast medium injection. An adrenal magnetic resonance image (MRI) scan showed

an oval-shaped tumor of the left adrenal gland that was inhomogeneously hypointense in the T1- and T2-weighted images. These findings indicated that the tumor could be an adenoma, and subtle abnormalities of the hypothalamo-pituitary-adrenal axis were present in this case because of the results of the cortisol value at 9 PM and the overnight 1 mg dexamethasone suppression test. Because the patient refused to undergo a surgical removal of the adrenal tumor, we decided to carry out passive observation.

Three months later, a hormonal study surprisingly documented undetectable ACTH levels and the same result was found after repeating this study. The patient was re-admitted to our department for further endocrinological evaluation. The clinical examination showed a normal weight (BMI 23.8 kg/m²), no edema, normotension (136/84 mmHg), no hirsutism, acne, or other signs of hypercortisolism. An abdominal CT scan confirmed the presence of a left adrenal mass which had not changed in comparison to the previous CT scan findings. The plasma cortisol level was normal, but an abnormal circadian rhythm was observed (0900h 9.5 μ g/dl, 1700h 6.3 μ g/dl, 2100h 7.1 μ g/dl) and was not suppressed completely by either 1 mg or 8 mg overnight dexamethasone (5.6 μ g/dl, 3.8 μ g/dl). The ACTH levels were below 5pg/dl. Other hormonal evaluation documented a normal urinary cortisol, 17-OHCS, and 17-KS (19.3 μ g/day, 6.9 mg/day, 2.1 mg/day). The plasma aldosterone and PRA were within the normal range (71.3 pg/dl, 1.1 ng/ml/hr). Adrenal scintigraphy using ¹³¹I-labeled adosterol revealed a positive uptake in the left adrenal tumor with no uptake in the right adrenal gland. These findings indicated that the production of cortisol in the adrenal tumor was not regulated through the hypothalamo-pituitary-adrenal axis.

The patient underwent a left laparoscopic adrenalectomy, during which the surface of the tumor was found to be smooth and not adherent to the kidney. The clinical course was unevent-

ful, and the patient was subsequently discharged on postoperative day 14. During the 6-month postoperative follow-up, hydrocortisone (5 mg/day) was administered as replacement therapy, even though this regimen is scheduled to be discontinued in the near future.

Morphologic Findings

The maximal diameter of the left adrenal tumor was 3.6 cm. The cut surface of the tumor showed solid lobulated yellowish nodules. The non-neoplastic area of the adrenal gland was atrophic (Fig. 2). Histological examination revealed that the tumor was arranged in island-like structures or focal cluster of small compact cells

surrounded by clear cells of a predominant cell type. Small compact cells were also arranged in a cord-like pattern. The nuclei, in most part, were small with no mitotic figures. It had histopathological features in common with ACTH-independent macronodular adrenocortical hyperplasia, including clear cell predominance, a pattern of small compact nests in clear cell areas, and a cord-like arrangement of small compact cells. Non-neoplastic area of the adrenal cortex is atrophic, without nodularity (Fig. 3).

In situ Hybridization

In situ hybridization to P-450scc, 3 β -HSD, P-450c21, P-45011 β , and P-45017 α were per-

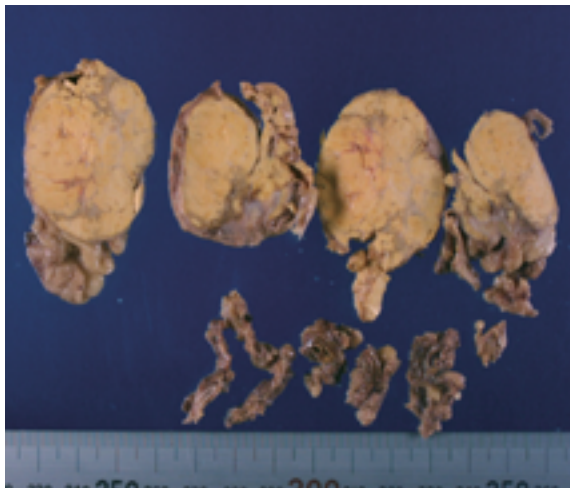


Fig. 2 Macroscopic specimens of the adrenal gland in the present case. The cut surface of the tumor was yellow, lobulated and encapsulated. The non-neoplastic area of the adrenal was atrophic.

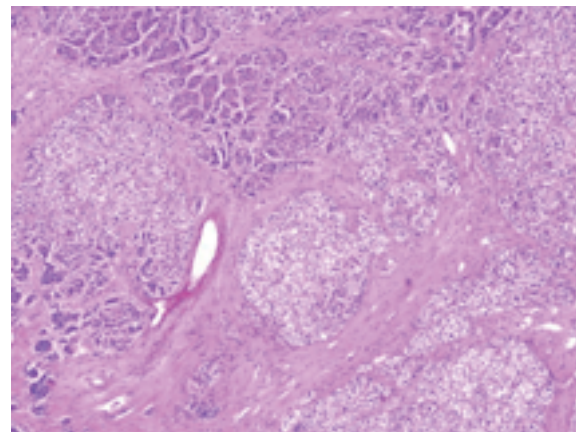


Fig. 3 Microscopically findings of the adrenal gland in the present case. The nodules were composed predominantly of clear cells and a focal cluster of compact cells. H-E stain. X100.

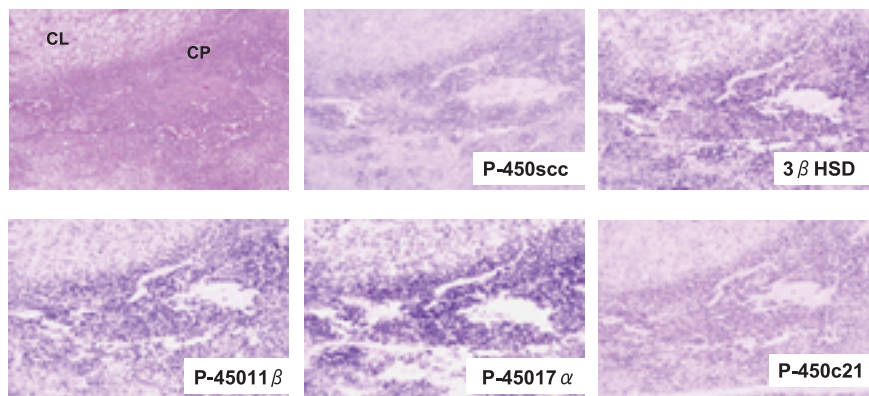


Fig. 4 *In situ* hybridization study of steroidogenic enzymes in the adrenal adenoma. Hybridization signals of the steroidogenic enzymes (P-450scc, 3 β HSD, P-45011 β , P-45017 α and P-450c21) were predominantly observed in compact cells. CP: compact cells, CL : clear cells

formed in this case. The details of the procedure of an in situ hybridization have already been reported by the authors¹⁰⁾¹¹⁾. The hybridization signals of P-450scc, 3 β -HSD, P-450c21, P-45011 β , and P-45017 α were predominantly observed in the compact cells (Fig. 4). No specific hybridization signal was obtained by employing the sense DNA probe instead of the anti-sense probe.

Discussion

The recommendations for the follow-up of patients with adrenal incidentalomas are designed to detect malignant and hypersecreting tumors¹²⁾¹³⁾. However, the management of incidentalomas is complicated by the lack of effective diagnostic procedures. Controversy still remains regarding the optimal follow-up strategy due to the fact that the data are based on a limited number of studies, often including only a small group of patients with variable follow-up times¹⁴⁾¹⁵⁾.

In the literature, a broad disparity has been reported regarding the prevalence of preclinical Cushing's syndrome (PCS). This discrepancy is mostly due to the fact that the applied criteria for the definition of PCS vary among the different studies¹⁶⁾. There is a wide spectrum of biochemical abnormalities that can be seen in patients with PCS. There is no single diagnostic test that can evaluate the entire patient for abnormalities of cortisol secretion. In studies employing the overnight 1 mg dexamethasone suppression test (DST), the reported prevalence of PCS ranges from 1% to 47%, whereas when two or more abnormal tests are required, the prevalence of PCS ranges from 5.7% to 24%^{17)~20)}. Until unquestionable criteria for the definition of PCS, as related to adverse clinical implications, can be obtained, then the true prevalence of autonomous cortisol production by adrenal incidentalomas will remain unknown.

The patient in this case had no specific clinical manifestation of Cushing's syndrome during the clinical course. At first admission, the blood

cortisol levels were almost normal excluding the value at 9 PM slightly rising with the maintenance of the circadian pattern and the blood ACTH level at 0900 h was in the normal range. In addition, the urinary excretion of 17-OHCS, 17-KS, and free cortisol were not increased. Nevertheless, the serum cortisol level at 0900 h was not completely suppressed by 1 mg of dexamethasone administration (4.0 μ g/dl). These findings indicated that subtle abnormalities of the pituitary-adrenal axis were present. Three months later, the ACTH was unexpectedly suppressed to low levels and the same result was observed when the study was repeated. Further hormonal investigations revealed the plasma cortisol to be normal, but it had an abnormal circadian rhythm (0900h 9.5 μ g/dl, 1700h 6.3 μ g/dl, 2100h 7.1 μ g/dl) and was not completely suppressed either by 1 mg or 8 mg overnight dexamethasone (5.6 μ g/dl, 3.8 μ g/dl) and the plasma ACTH levels were below 5pg/dl. The levels of urinary cortisol, 17-OHCS, and 17-KS were in the normal ranges. Adrenal scintigraphy using ¹³¹I-labeled adosterol revealed a positive uptake in the left adrenal tumor with no uptake in the right adrenal gland. CT scans confirmed the presence of a left adrenal mass which had not changed in size and nature in comparison to previous CT scan findings. These findings indicated that the production of cortisol in the adrenal tumor was not regulated through the hypothalamo-pituitary-adrenal axis.

The natural history of PCS remains unknown, and it is thought that the progression of PCS is very slow, and that it takes several years to lose the diurnal plasma ACTH and cortisol rhythm, for the plasma ACTH to become undetectable, and for the plasma cortisol level to increase. The loss of the normal diurnal rhythm was considered to be the most sensitive indicator in the transition from a nonhyperfunctioning adrenal cortical adenoma to a clinically silent but hyperfunctioning one. Therefore, paired circadian cortisol and ACTH levels should be part of the workup for

patients with adrenal incidentalomas^{2)21)~24)}. As ACTH is suppressed at low levels, which is thus considered to be an indication for surgery, the CRH test thereafter becomes progressively more abnormal, and finally the excretion of urinary cortisol exceeds the normal range²⁵⁾²⁶⁾. Of course, it should be noted that commercially available ACTH assays are unreliable for estimating low ACTH concentrations.

Recently, Libe et al. demonstrated a cumulative risk of developing endocrine abnormalities of 17% at 1 year, 29% at 2 years, and 47% at 5 years, with a higher risk in the first 2 years of follow-up if the initial tumor size was > 3 cm²⁰⁾. In the study by Barzon et al, the estimated cumulative risks of developing hyperfunction were 4% after 1 year, 9.5% after 5 years, and 9.5% after 10 years¹⁷⁾. Thus a mass measuring 3 cm or more in diameter at diagnosis and exclusive radiocholesterol uptake by the mass via scintigraphy have been reported to be important risk factors for the occurrence of adrenal hyperfunction⁸⁾. It is thought that the patient in this case has a high risk of worsening autonomous cortisol secretion, because the size of the left adrenal incidentaloma was 45 mm \times 33 mm in diameter and a positive uptake in the adrenal tumor using ¹³¹I-labeled deoxysterol scintigraphy was detected with no uptake in the right adrenal gland, thus a more detailed and careful follow-up should be recommended for such a case at least within half a year from the first inspection.

The histological analysis in this case confirmed the diagnosis of ACTH-independent macronodular adrenocortical hyperplasia (AIMAH), including clear cell predominance, a pattern of small compact nests in clear cell areas, and a cord-like arrangement of small compact cells. The clinical characteristics of AIMAH include male dominance, low plasma ACTH, autonomous cortisol production, bilateral adrenal nodular masses and no pituitary abnormalities. However the etiology and the natural history of this disease have not been elucidated, it is speculated that the bilateral adrenal tumors had existed for many years²⁷⁾.

Thus careful long-time follow-up should be also recommended in this case even when no bilateral adrenal mass is detected.

In addition we investigated the localization of the steroidogenic enzymes in the adrenal tumor using in situ hybridization methods. The tumor in this case therefore had the capacity of producing cortisol, the same as in functioning tumors. It has previously been demonstrated by immunohistochemical and in situ hybridization studies of the enzymes involved in corticosteroidogenesis, that the steroidogenic enzymes including 3β -HSD, P-450c21, P-45011 β , and P-45017 α were expressed in adrenocortical tumors, not only in overt Cushing's syndrome, but also in the great majority of hormonally inactive adrenocortical neoplasms. Furthermore, the immunohistochemical and in situ hybridization pattern of steroidogenic enzyme expression, as well as steroid secretion patterns varied markedly among the cases of incidentalomas studies^{28)~31)}. As shown in this case, a more detailed and careful follow-up should thus be recommended in patients who do not need surgery or who refuse the surgical removal at first presentation, because the endocrine findings in patients with PCS were heterogeneous, which may be explained by the variable amounts and variable durations of cortisol secretion by such tumors.

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(和文抄録)

短期間のうちにコルチゾールの自律的分泌能が 明確となった副腎偶発腫瘍の一例

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症例は57歳、女性。45 mm x 33 mmの左副腎偶発腫瘍の精査目的で当科に入院となった。高コルチゾール血症による身体所見は認めず、内分泌学的検査では、コルチゾールの夜間9時の値が軽度上昇している以外は、ACTH、コルチゾール値ともほぼ正常で日内リズムも保たれていた。しかしデキサメサゾン 1mg 抑制試験ではコルチゾールは完全には抑制されなかった。よってわずかな間脳下垂体副腎系の異常が示唆され、腫瘍径も4cmを超えており摘出も検討したが、患者さんは保存的経過観察を希望され手術は施行しなかった。ところが3ヶ月後の血液検査でACTH値は感度以下の低値で、コルチゾール基礎値は正常であるが、デキサメサゾン 1mg または 8mg 抑制試験でコルチゾールは完全に抑制されなかった。アドステロール副腎シンチグラフィー検査では左副腎腫瘍に高集積を認め、右副腎には集積を認めなかった。そこで今回患者さんの同意を得て腹腔鏡下で左副腎摘出術を施行した。摘出副腎腫瘍は光顕像ではACTH-independent macronodular adrenocortical hyperplasia (AIMAH)の組織像であり、*in situ* hybridization study ではcompact cellにより強いP-450scc, 3 β -HSD, P-450c21, P-45011 β そしてP-45017 α のシグナルが認められた。本症例は短期間のうちにコルチゾールの自律的分泌能が明確となった副腎偶発腫瘍の一例であり、より注意深い、詳細な、短期間のうちの内分泌学的経過観察が副腎偶発腫瘍に対して必要であることが示唆された。