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【 CASE REPORT 】

Ectopic Cortisol-producing Adrenocortical Adenoma Detected by 131I-6β-iodomethyl-norcholesterol Scintigraphy

Seisuke Sato[1], Hitomi Imachi[1], Toshihiro Kobayashi[1], Kensaku Fukunaga[1], Jingya Lyu[1], Tao Dong[1], Yuuki Yoshioka[1], Takanobu Saheki[1], Youko Fukata[1], Natsuki Ban[1], Kurumi Urushihara[1], Kyuuichi Kadota[2] and Koji Murao[1]

Abstract:
A 50-year-old man was referred to our department for overt Cushing's syndrome (CS). His plasma cortisol concentrations were 314 μg/L, and his urinary cortisol concentrations were 431 μg/day. The plasma adrenocorticotropic hormone (ACTH) concentration was below the detectable limit. Computed tomography revealed atrophy of both adrenal glands and the presence of a left pararenal tumor. 131I-6β-iodomethyl-norcholesterol scintigraphy showed an intense uptake by the left pararenal tumor. These findings suggested that the left pararenal tumor was ectopic cortisol-producing adrenocortical adenoma. This case serves as a reminder that 131I-6β-iodomethyl-norcholesterol scintigraphy is an effective method for diagnosing ACTH-independent CS in which no adrenal tumor has been found.

Key words: ectopic adrenocortical adenoma, cortisol-producing adrenocortical adenomas, Cushing's syndrome, scintigraphy

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Introduction

Cushing's syndrome (CS) is caused by excess adrenal glucocorticoid secretion that is adrenocorticotropic hormone (ACTH)-dependent or independent. The latter is often divided into five subtypes: adrenocortical adenoma, adrenocortical carcinoma, primary pigmented nodular adrenal disease, primary macronodular adrenal hyperplasia, and ectopic adrenocortical adenoma (EAA). Ectopic cortisol-producing adrenocortical adenoma (CPA) is extremely rare. Occasionally, ectopic adrenal tissues undergo marked hyperplasia and develop into EAA, but to our knowledge, only eight such cases have been reported.

We herein report a case in which 131I-6β-iodomethyl-norcholesterol scintigraphy greatly contributed to the diagnosis of EAA.

Case Report

A 50-year-old Japanese man was referred to our department for overt CS, presenting with facial erythrosis, buffalo hump, central obesity, abdominal red striae, easy bruising, hypertension, and diabetes mellitus. Ten years earlier, a tumor around the kidney had been found, and biopsy revealed it to be benign. Abdominal computed tomography (CT) performed before his referral to our department did not show an adrenal tumor.

His plasma cortisol concentrations were 314 μg/L (normal: 62-180 μg/L) in the morning and 253 μg/L at midnight. His urinary cortisol concentration was 431 μg/day (normal: 11.2-80.3 μg/day). The morning plasma ACTH concentration was below the detectable limit. We performed the 0.5-mg overnight dexamethasone suppression test, after which the morning plasma cortisol was not suppressed (239 μg/L). The levels of other serum steroids were low

[1]Department of Endocrinology and Metabolism, Faculty of Medicine, Kagawa University, Japan and [2]Department of Pathology, Faculty of Medicine, Kagawa University, Japan
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Correspondence to Dr. Seisuke Sato, seisuke-310@med.kagawa-u.ac.jp

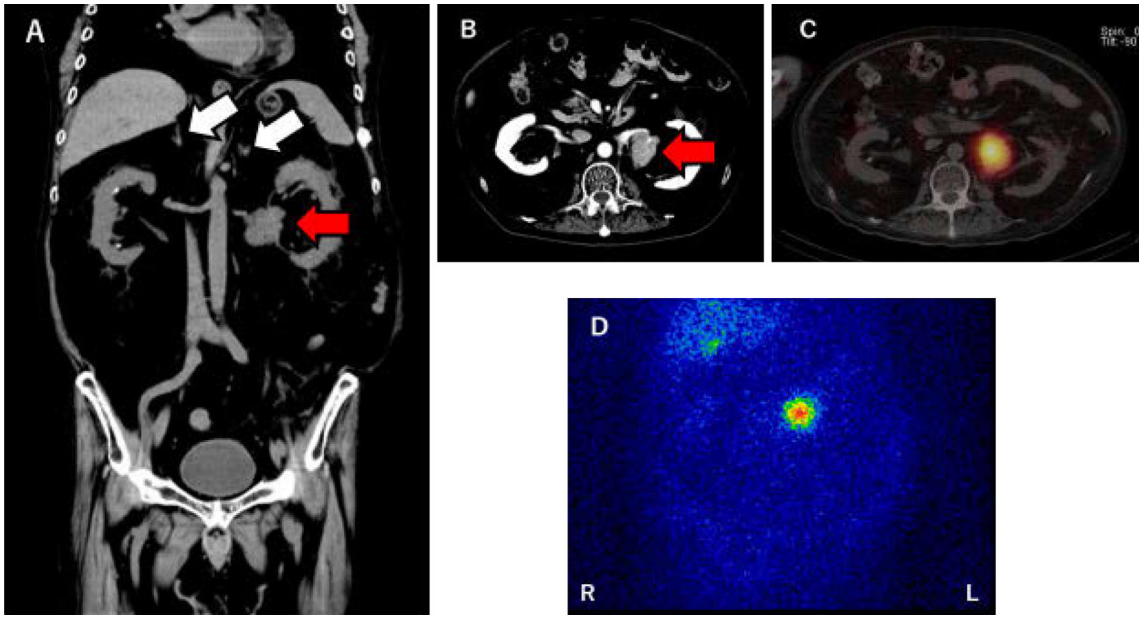

Figure 1. **A: Coronal section of CT showing that both adrenal glands were normal, and an unknown tumor was found in the left renal hilus. White arrows: normal adrenal gland, red arrow: pararenal tumor. B, C: Axial section of CT and 131I-6β-iodomethyl-norcholesterol scintigraphy. 131I-6β-iodomethyl-norcholesterol scintigraphy showing an intense uptake by the left pararenal tumor. D: Planar image of 131I-6β-iodomethyl-norcholesterol scintigraphy.**

(DHEA-S 105 ng/mL, renin activity 1.2 ng/mL/h, aldosterone 2.2 ng/dL, and free testosterone 5.6 pg/mL). The results of a routine serum biochemical examination were unremarkable, except for hypokalemia and low levels of total protein and albumin. This patient was diagnosed with ACTH-independent CS based on his clinical symptoms and the results of endocrinologic examinations.

CT revealed atrophy of both adrenal glands and the presence of a left pararenal tumor, measuring 40 mm in diameter. This tumor had no continuity with the left adrenal gland. Magnetic resonance imaging (MRI) showed that this tumor had a rich lipid inside. 131I-6β-iodomethyl-norcholesterol scintigraphy showed an intense uptake of the tracer by the left pararenal tumor (Fig. 1), and the tracer uptake was suppressed in both adrenal glands. These findings suggest that the left pararenal tumor was ectopic CPA. Pituitary MRI and thyroid sonography did not show any abnormalities.

The left kidney and tumor were resected (Fig. 2A, B). The pathological findings of this tumor were an eosinophilic cytoplasm, Weiss score 2, and positive infiltration of the capsule. Hematoxylin-Eosin staining did not show the normal three layers of the adrenal cortex, but it instead only showed the neoplastic zona fasciculata (Fig. 2C). The tumor was strongly stained by the steroid synthase CYP17A1 (Fig. 2D), suggesting that this tumor was derived from the adrenal cortex. The tumor was ultimately diagnosed as ectopic CPA.

Resection of the tumor eliminated the clinical symptoms of CS. The excised lesion included only the cortical component, not the medullary component. In addition, adrenal-derived tissues were not found in adipose tissue around the resected joint at the time, so it was believed that the lesions had been ectopic. Postoperatively, glucocorticoid supplementation was necessary. One week after the operation, the patient needed 30 mg of hydrocortisone. Six years after resection, the patient continued to take 5 mg hydrocortisone daily.

Discussion

Ectopic adrenal tissues have been reported from a variety of anatomic sites, including the celiac plexus, kidney, testis, epididymis, broad ligament, canal of Nuck, hernial and hydrocele sacs, mesoappendix, liver, lung, intradural space, and brain (1). The adrenal cortex originates from the intermediate mesoderm during embryonic development, and at the fifth week of gestation, the mesoblast begins to proliferate and differentiate, eventually forming adrenocortical cells. Fragments of adrenocortical tissue are scattered along the migration path, forming the ectopic adrenal glands (2).

Histologically, the ectopic adenoma in our case was composed of clear cells and compact cells, which is consistent with the characteristics of adrenal CPA (3). It is generally thought that the clear cells mainly function in the storage of steroid hormone precursors, while the compact cells actually synthesize these precursors (4). A previous report indicated that the ultrastructure and steroidogenic enzyme profile of ectopic adenoma were similar to those of adrenal CPA, suggesting that these tumors were derived from the same cells.

Table summarizes the cases of previous reports of ectopic CS (5-12). Almost all of the tumors were located near the kidney, and most tumors were over 3 cm in size. The size

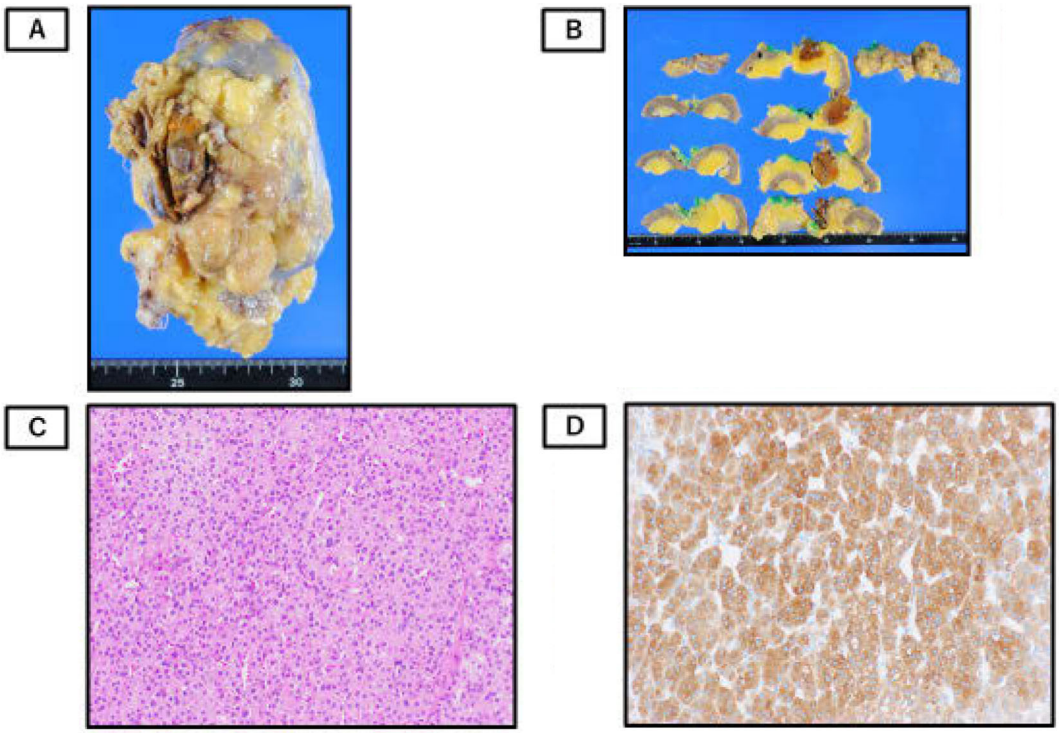

Figure 2. **A, B: The removed tissue is covered with adipose tissue; the brown part is tissue of the ectopic CPA. C: Hematoxylin and Eosin staining of the tumor. D: Immunostaining of CYP17A1.**

Table. **Case Reports of Ectopic Adrenocortical Adenoma.**

Case	Reference	Sex	Age	Largest diameter of tumor(cm)	Location of the tumor	Recurrence
1	5	F	33	3.0	Next to left adrenal	Local recurrence 4 years after surgery
2	6	F	63	3.5	Left renal hilum	no description
3	7	F	35	3.8	Left pararenal	no description
4	8	M	38	5.3	Anterior of left renal hilum	no description
5	9	F	53	3.5	Left renal hilum	Local recurrence 2 years after surgery
6	10	F	27	2.5	Left renal hilum	followed up for 3 months
7	11	F	37	2.99	Right renal sinus	followed up for 1 month
8	12	F	18	3.0	Left renal hilum	followed up for 12 months
9	our case	M	50	4.0	Left pararenal	followed up for 6 years

and cortisol production ability are believed to be correlated, so it is difficult to locate the tumor until it reaches a certain size. Previous reports have indicated that oral steroids were discontinued within one year. This report describes the case with the longest postoperative follow-up to date, and hydrocortisone is still being administered nine years later. After surgery, hormone replacement therapy may be required for a long time.

We herein report the case of a man with intact adrenal glands who presented with spontaneous ACTH-independent CS caused by an ectopic adrenocortical adenoma located in the renal hilum, a rare site for the occurrence of this tumor, which may have easily led to its misdiagnosis as renal cancer and therefore to radical nephrectomy. It is well known that conventional planar 131I-6β-iodomethyl-norcholesterol scintigraphy has a low sensitivity for the detection of small lesions, especially when the physiological gallbladder and bowel radiotracer accumulation is superimposed. Recently, single-photon emission computed tomography (SPECT) has been shown to improve the image resolution of smaller lesions with an increased sensitivity without reducing the specificity. Performing a qualitative pattern analysis by SPECT can be an effective approach for identifying adrenal glands or distinguishing the tracer uptake from the liver, gallbladder, and colon. In addition, SPECT can be used to perform a quantitative analysis of the adrenocortical uptake (13). In the present case, 131I-6β-iodomethyl-norcholesterol scintigraphy was quite useful for distinguishing adrenal CS due to an adrenal tumor, suggesting that 131I-6β-iodomethyl-norcholesterol scintigraphy is extremely useful for the differentiation diagnosis of ectopic adrenal adenoma.

In conclusion, we encountered a patient with intact adrenal glands who presented with ACTH-independent CS caused by an ectopic adrenal adenoma. 131I-6β-iodomethyl-norcholesterol scintigraphy was quite useful for diagnosing ectopic CPA.

The authors state that they have no Conflict of Interest (COI).

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