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【 CASE REPORT 】

A Rare Case of Ectopic Adrenocorticotropic Hormone Syndrome with Recurrent Olfactory Neuroblastoma

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Abstract:

A 40-year-old woman who had a history of recurrent olfactory neuroblastoma presented with full moon face, central obesity, buffalo hump, impaired glucose tolerance and bilateral cervical lymph node swelling. Laboratory tests showed morbidly elevated levels of adrenocorticotropic hormone (ACTH) and cortisol, which were not suppressed by high-dose (8 mg) dexamethasone. Biopsies of the enlarged cervical lymph nodes revealed ACTH-positive metastatic olfactory neuroblastoma, and ectopic ACTH syndrome was diagnosed. Metyrapone was used to suppress cortisol production and resulted in decreased levels of ACTH and cortisol. Bilateral cervical tumor resection further reduced the ACTH and cortisol levels, accompanied by a reduction in the metyrapone dosage. Cushing's syndrome was alleviated through ACTH-producing tumor removal.

Key words: ectopic ACTH syndrome, olfactory neuroblastoma, adrenocorticotropic hormone, Cushing's syndrome, metyrapone

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Introduction

Ectopic adrenocorticotropic hormone (ACTH) syndrome causes hypercortisolemia as a result of secondary increases in ACTH due to ACTH-producing tumors (1, 2). The clinical features include carbohydrate metabolism, hypokalemia, proximal myopathy, hypertension and hyperpigmentation. Olfactory neuroblastomas (ONBs) are rare tumors that arise from the olfactory epithelium. They may occasionally develop paraneoplastic syndrome, and more than 28 cases associated with ectopic ACTH syndrome (3) have been reported (3-13).

We herein report an additional rare case of ectopic ACTH syndrome with recurrent ONB nine years after initial therapy.

Case Report

At 31 years old, a woman was first diagnosed with topical olfactory neuroblastoma at a local hospital. The tumor was surgically removed but recurred six years later, at which point it was again resected with the addition of topical radiation therapy. At 40 years old, she developed central obesity, hypokalemia, leukocytosis, and diabetes mellitus. She was referred to our hospital for suspected Cushing's syndrome and hospitalized with the complaint of muscle weakness. The patient had a history of high blood pressure, without any medication and no remarkable relevant family history.

A physical examination at admission showed a height of 166.5 cm, weight 108.7 kg and body mass index 39.2 kg/m^2. Her blood pressure was 151/82 mmHg. Moon face, buf-

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Table. Results of Blood Test at Time of Hospitalization. Hypokalemia and High Values of Adrenocorticotropic Hormone and Cortisol were Confirmed.

	Reference range	Values
WBC, /μL	2,700-8,800	7,300
Neutro, %	42.0-74.0	87.5
Eosino, %	<6.0	0.0
Baso, %	<2.0	0.0
Mono, %	2.0-8.0	3.3
Lympo, %	19.0-47.0	9.2
RBC, /μL	$3.7\text{-}5.4\times10^6$	4.68×10^6
Hb, g/dL	11.0-17.0	14.2
PLT, /μL	$140\text{-}340\times10^3$	127×10^3
ALB, g/dL	3.9-4.9	3.3
AST, U/L	8-38	21
ALT, U/L	4-44	54
ALP, U/L	104-338	117
LD, U/L	106-211	461
T-Bil, mg/dL	0.2-1.2	1.19
Blood glucose, mg/dL	60-110	203
HbA1c, %	4.6-6.2	7.2
BUN, mg/dL	8.0-22.6	20.1
Cr, mg/dL	0.4-0.8	0.65
eGFR, mL/min/1.73 m^2		70.7
Na, mEq/L	138-148	145
K, mEq/L	3.6-5.2	1.9
Ca, mg/dL	8.2-10.2	7.1
P, mg/dL	2.5-4.7	2.9
Cortisol, μg/dL	6.2-18.0	49.1
ACTH, pg/mL	7.2-63.3	440.8
Intact PTH, pg/mL	10-65	148
TSH, μIU/mL	0.50-5.00	0.29
FT3, pg/mL	2.30-4.30	1.82
FT4, ng/dL	0.90-1.70	0.94

WBC: white blood cell, Neutro: Neutrophil, Baso: basophil, Mono:monophil: Lympo: lymphocyte: RBC: red blood cell: Hb: hemoglobin, PLT: platelet, ALB: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LD: Lactate dehydrogenase, T-Bil: total bilirubin, HbA1c: hemoglobin A1c, BUN:blood urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration rate, Na: sodium, K: potassium, Ca: calcium, P: phosphate, ACTH: adrenocorticotropic hormone, PTH: parathyroid hormone, TSH: thyroid stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine

falo hump with enlargement of cervical lymph nodes along with the pitting edema in both lower limbs and gentle pigmentation of the fingertips were noted. Thoracoabdominal radiography, an electrocardiogram and bone density measurement revealed no abnormal findings.

Laboratory tests showed increased neutrophils, impaired glucose tolerance and marked hypokalemia (Table). Endocrinological data revealed markedly elevated levels of plasma ACTH and serum cortisol. Urinary excretion of free cortisol was also markedly elevated (1,100 μg/day). Serum cortisol did not show any diurnal variation, and overnight dexamethasone at 1 and 8 mg did not suppress the serum cortisol levels. Corticotropin-releasing hormone (CRH) loading failed to evoke an ACTH response. Low T3 syndrome was observed.

Head magnetic resonance imaging showed no abnormal findings in the pituitary gland. Cervical contrast computed tomography (CT) showed an enhancing bilateral tumor with a contrast effect 40 mm in diameter on the right and 36 mm on the left (Fig. 1).

Octreotide scintigraphy was performed because of the suspicious neuroendocrine nature of the tumor, which showed the accumulation in the bilateral cervical lymph nodes, cerebral skull, anterior mediastinum and bones (Fig. 2).

The patient underwent a cervical lymph node biopsy during the hospitalization, and findings of cervical lymph node tumors showed histopathological recurrent ONB with formed lobules, separated by hyalinized fibrous stroma, and pseudo-rosettes (Homer Wright rosettes) with neoplastic cells palisading around the central fibrillar neural matrix were present (Fig. 3). The cells were almost uniform, with sparse cytoplasm and round nuclei with punctate chromatin. The Ki-67 labeling index reached 10%. An immunohistochemical analysis showed that the tumor was positive for CD56, chromogranin A and synaptophysin (Fig. 4).

ACTH immune staining was positive in the specimens, but the specimens from the 2008 and 2014 surgeries showed no ACTH immunostaining (Fig. 5).

Since she had very high levels of serum cortisol, metyrapone, a steroid synthesis inhibitor, was started at 1,000 mg daily, gradually increased to 2,000 mg on the 13th day. Hydrocortisone was supplemented on the 20th day. Metyrapone administration decreased both the plasma ACTH level and urine excretion of cortisol. Following daily administration of 2,000 mg metyrapone and 25 mg hydrocortisone, the serum cortisol level decreased close to the normal range. Changes in the serum cortisol level and urinary excretion of cortisol during hospitalization are shown in Fig. 6. Hypokalemia was improved following the oral administration of 1,800 mg daily potassium chloride (discharged at a rate of 3.5 mEq/L). Insulin and diet therapy were initiated, but before discharge, insulin therapy was discontinued, and pre-prandial glucose levels were maintained at 100 mg/dL without oral hypoglycemic agents.

At three months after discharge, the bilateral lymph node mass was resected. After the removal of the cervical mass, the ACTH levels declined markedly, and the metyrapone dose was gradually reduced to 500 mg/daily, with good ACTH and cortisol control achieved (plasma ACTH: 24 pg/mL, serum cortisol: 2.7 μg/dL) at 6 months after surgery.

Discussion

We reported a case of ONB that showed Cushing's syndrome nine years after the initial diagnosis. A further examination revealed ACTH production from metastasized cervical lymph node masses. Symptoms of Cushing's syndrome were brought under control with surgery and medication, includ-

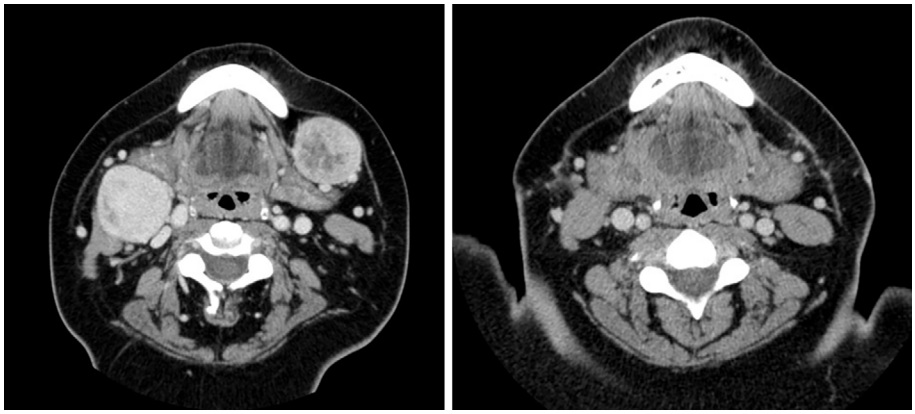

Figure 1. Contrast computed tomography of the head and neck during hospitalization. (A) Cervical lymph node masses showed a contrast effect of 40 mm on the right and 36 mm on the left. (B) Image after the extraction of bilateral cervical lymph nodes.

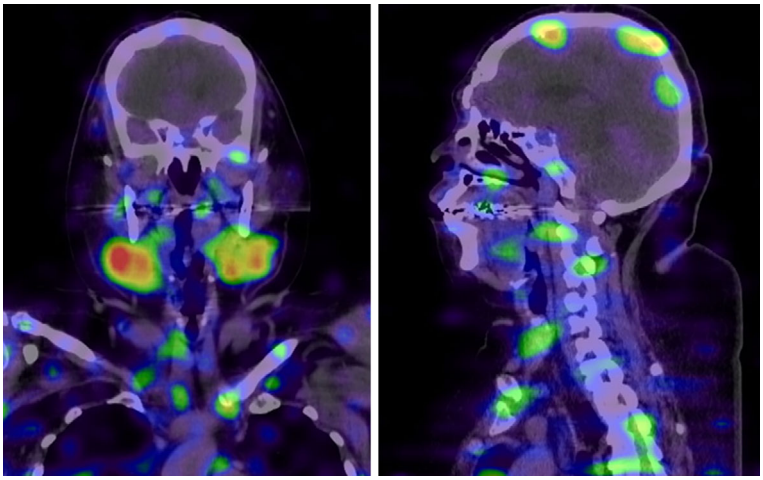

Figure 2. Octreotide scintigraphy during hospitalization. The accumulation was seen in both cervical lymph nodes, the cerebral skull, anterior mediastinum and bones.

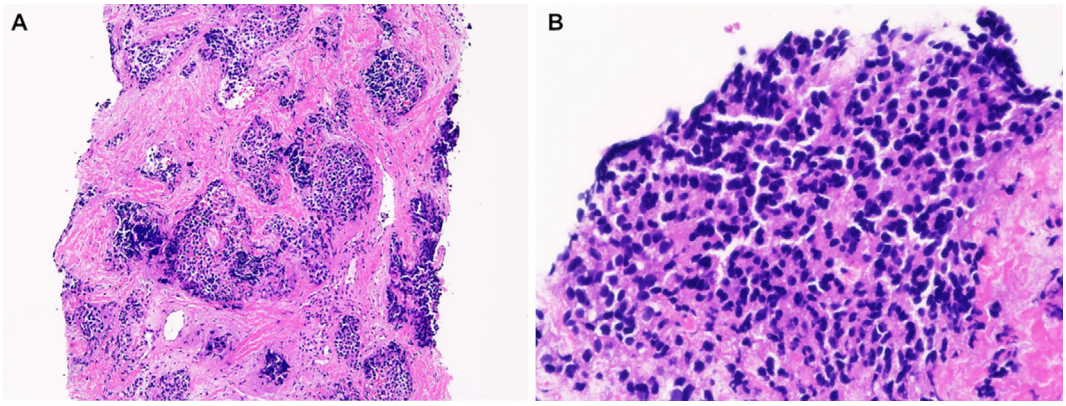

Figure 3. A left cervical lymph node biopsy of the tumor showing a histologically alveolar-like structure, accompanied by a neurofibril matrix-like image histologically similar to that of previous olfactory neuroblastoma specimens. Subsequently, this was diagnosed as lymph node metastasis of olfactory neuroblastoma. (A) Hematoxylin and Eosin (H&E) staining, 100× magnification. (B) H&E staining, 400× magnification.

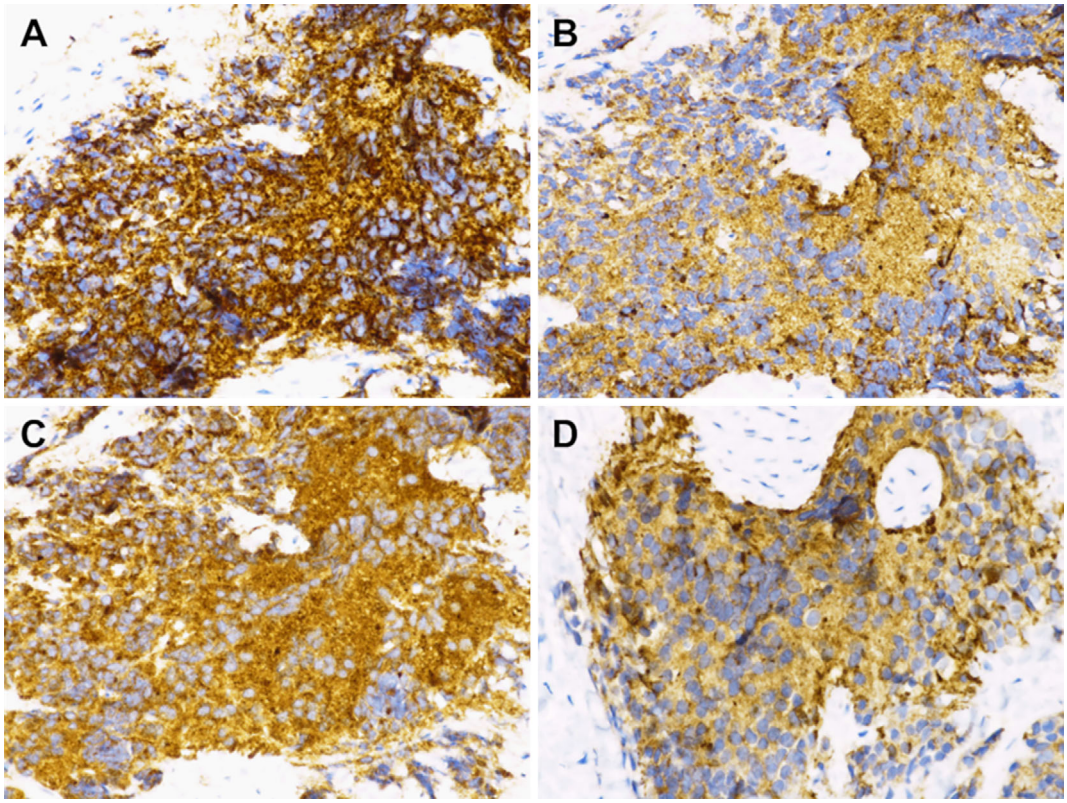

Figure 4. **Immunohistochemistry staining for synaptophysin. Immunohistochemistry results were positive for CD56, chromogranin A, synaptophysin and adrenocorticotropic hormone (ACTH). (A) CD56, 400× magnification. (B) Chromogranin A, 400×magnification. (C) Synaptophysin, 400× magnification. (D) ACTH, 400× magnification.**

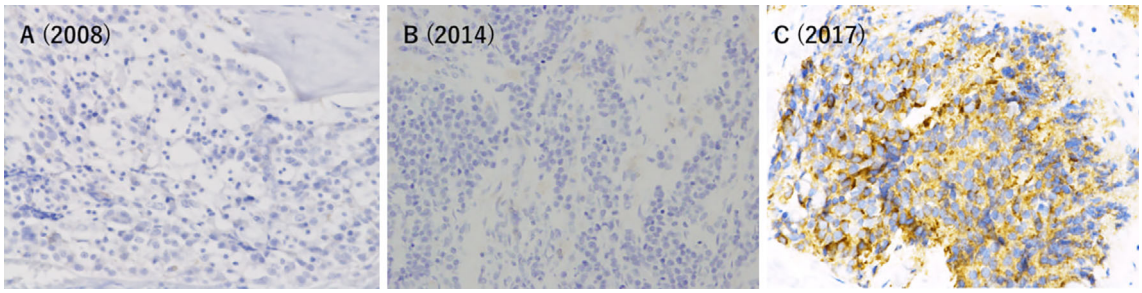

Figure 5. **Changes in adrenocorticotropic hormone immunohistochemistry ×400. (A) Specimen of olfactory neuroblastoma at the first occurrence in 2008. (B) Specimen of olfactory neuroblastoma at the second occurrence in 2014. (C) Biopsy specimen of cervical lymph nodes at the time of recurrence in 2017.**

ing metyrapone.

This case highlighted the relationship between ONB and ectopic ACTH syndrome. Lung tumors account for approximately half of other tumor types that cause ectopic ACTH syndrome (7), followed by pancreatic and thymic tumors (8). There are also reports that ONBs are related to approximately 10% of ectopic ACTH syndrome cases (3, 9).

In the present case, the tumor produced ACTH not at the initial stage but rather at recurrence of Cushing's syndrome. This patient demonstrated ectopic ACTH syndrome of a metastatic tumor that occurred nine years following the initial onset of ONB.

Kadoya et al. reported a case study on ectopic ACTH syndrome that occurred at the time of ONB recurrence (10-13). They proposed several hypotheses as to why Cushing's syndrome developed when it recurred years after its initial onset. First, it is possible that the ONB tumor cells dedifferentiated and transformed to ACTH-producing cells. There have been reports of similar cases in which the hormone secretion of tumors changed over extended periods of time (14). Second, there may have been a change in the ACTH production resulting from the enhancement of the

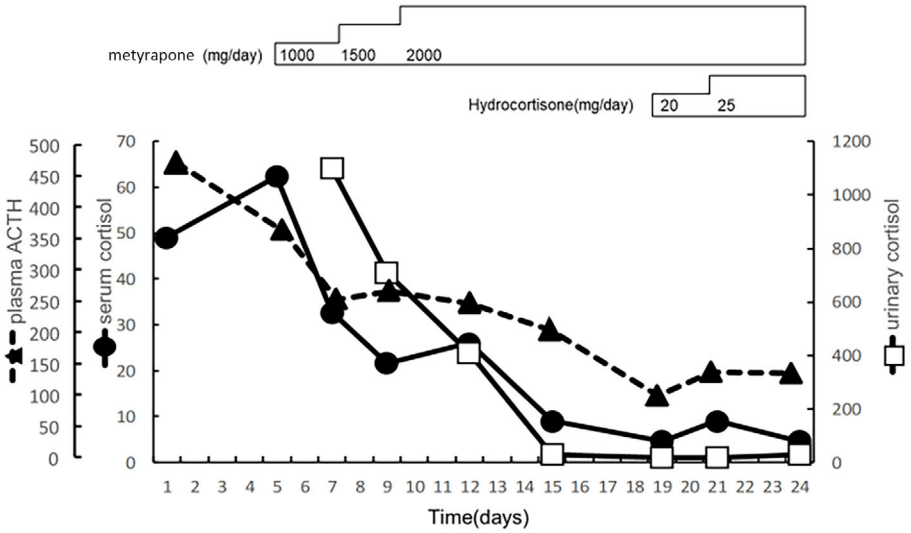

Figure 6. Changes in plasma adrenocorticotropic hormone and serum cortisol levels and urinary cortisol during hospitalization.

proopiomelanocortin (POMC) gene expression.

In this case, it was confirmed that ACTH was decreased following the administration of metyrapone prior to the excision of the ACTH production site. Following metyrapone administration, the plasma ACTH levels usually increase in patients with pituitary Cushing's disease but decrease in those with ectopic ACTH syndrome (15, 16). Cyclic Cushing's syndrome may have influenced the decrease in the ACTH levels, although glucocorticoid-driven positive-feedback regulation in ectopic ACTH syndrome has also been proposed (17).

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

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