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【 CASE REPORT 】

Somatostatin Receptor-negative and Fluorodeoxyglucose-positron Emission Tomography-positive Lung Neuroendocrine Tumor G1 Exhibiting Cyclic Cushing's Syndrome

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Abstract:

Localization of ectopic cyclic Cushing's syndrome, which causes life-threatening complications, is challenging. A 70-year-old woman showed cyclic hypokalemia and hyperglycemia and was diagnosed with cyclic ectopic Cushing's syndrome. Although somatostatin-receptor scintigraphy failed to localize the responsible tumor, fluorodeoxyglucose-positron emission tomography (FDG-PET) showed the uptake of tracer in a lung tumor. Lobectomy resulted in remission. The resected adrenocorticotropic hormone (ACTH)-producing neuroendocrine tumor had Ki-67<2% and negative staining for somatostatin receptors. This is the first case assessed both radiological findings and pathological findings in cyclic ectopic Cushing's syndrome. Subsequent FDG-PET is recommended if somatostatin-receptor scintigraphy is negative.

Key words: cyclic, ACTH-producing tumor, somatostatin-receptor, FDG-PET

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Introduction

Cyclic Cushing's syndrome is defined as repeated appearance and remission of hypercortisolemia, which causes life-threatening immunocompromised, hypertensive, and hyperglycemic states (1). Of such cases, 54% and 26% are pituitary adenomas and ectopic adrenocorticotropic hormone (ACTH)-producing tumors, respectively. Small-cell lung carcinomas and bronchial or thymic carcinoid tumors are reported to be the most common ectopic ACTH-producing tumors (2). Proper localization is required for radical resection.

Whole-body radioisotope imaging can help localize the responsible tumor. Somatostatin-receptor (SSTR) scintigraphy is used for the localization of various neuroendocrine tumors (NETs), since the majority of NETs express SSTRs on their cell surface (3). Fluorodeoxyglucose-positron emission tomography (FDG-PET), which identifies malignant tumors by their high glucose uptake (4), is also helpful for localizing NETs, including ACTH-producing tumors (5). However, while the radiological findings of continuous ACTH-producing tumors are well reported, few studies have described the localization of ectopic ACTH-producing tumor showing cyclic ACTH production by the combination of these radioisotope imaging modalities. Furthermore, no report has included the complete radiological findings and immunohistolochemistry findings, including the SSTR expression. Some cases could not receive radical resection because their responsible tumors were unable to be localized (6, 7).

In the present report, the responsible tumor of a case of cyclic ectopic Cushing's syndrome was localized using both

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Table 1. Clinical Characteristics of the Patient in Peak or Trough Phase.

Parameters (unit)	Peak phase	Trough phase
WBC (/μL)	10,900	5,950
Neut (%)	77.6	65.8
Eosi (%)	0.1	1.8
Lym (%)	17.8	25.5
RBC (/μL)	4.66×10^6	3.62×10^6
Hb (g/dL)	14.4	11.3
Hct (%)	40.8	34.5
Plt (/μL)	18.1×10^4	19.8×10^4
AST (IU/L)	18	21
ALT (IU/L)	18	16
TP (g/dL)	5.6	5.7
BUN (mg/dL)	19.9	17.0
Cre (mg/dL)	0.60	0.68
Na (mEq/L)	145	145
K (mEq/L)	2.2	4.0
Cl (mEq/L)	97	111
Ca (mg/dL)	8.7	9.1
IP (mg/dL)	1.9	2.5
TG (mg/dL)	100	142
TC (mg/dL)	138	134
HDL-C (mg/dL)	54	33
FPG (mg/dL)	222	134
HbA1c (%)	9.4	7.4
PRA (ng/mL/h)	0.4	6.4
PAC (pg/mL)	49.2	40
TSH (μU/mL)	0.008	0.24
FT4 (ng/dL)	1.09	0.92
FT3 (pg/mL)	1.56	2.85
PRL (ng/mL)	11.3	14.6
LH (mIU/mL)	27.7	18.7
FSH (mIU/mL)	58.0	55.6
GH (ng/mL)	0.48	1.18
IGF-I (ng/mL)	107	51
ADH (pg/mL)	2.9	0.8

Neut: neutrophil, Eosi: eosinophil, Lym: lymphocyte, RBC: red blood cell, Hct: hematocrit, Plt: platelet, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TP: total protein, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, IP: inorganic phosphorus, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, FPG: fasting plasma glucose, DHEA-S: dehydroepiandrosterone sulfate, PRA: plasma renin activity, PAC: plasma aldosterone concentration, FT4: free thyroxine, FT3: free triiodothyronine, PRL: prolactin, LH: luteinizing hormone, FSH: follicle stimulating hormone, GH: growth hormone, IGF-I: insulin-like growth factor I, ADH: antidiuretic hormone

SSTR scintigraphy and FDG-PET. In addition, the immunohistochemistry findings of SSTRs in the resected tumor verified the findings of SSTR scintigraphy.

Case Report

A 70-year-old woman visited a hospital for weakness in her limbs. She also showed central obesity, buffalo hump, and fragile skin. Her systolic blood pressure was over 180 mmHg. Hypercortisolemia (44.9 μg/dL), hypokalemia (2.2 mEq/L), and exacerbation of diabetes mellitus were confirmed (Table 1). Her plasma ACTH level was dramatically high (135.0 pg/mL) despite high cortisol levels (Table 1, 2). Functional tests revealed a lack of ACTH/cortisol circadian rhythms and no suppression after an overnight low-dose (0.5 mg) or high-dose (8 mg) dexamethasone suppression test (DST) (Table 1, 2). She was thus diagnosed with ACTH-dependent Cushing's syndrome.

A pituitary tumor 4 mm in diameter was found by magnetic resonance imaging (MRI) (Fig. 1A). Corticotropin-releasing hormone (CRH) administration did not increase the ACTH levels (Table 3). Because the results of the high-dose DST and CRH loading test suggested that the responsible tumor was not located in the pituitary gland, we searched for ectopic lesions producing ACTH and found a small lung tumor 8.8 mm in diameter by computed tomography (Fig. 1D). Bilateral inferior petrosal sinus sampling (IPSS) was scheduled, but unexpectedly, her blood pressure, potassium levels, and plasma glucose levels normalized (Table 1), and the ACTH and cortisol levels decreased without any medication before IPSS was performed (Table 2). This calm period lasted for two years.

The patient was admitted to our hospital again for hypercortisolemia with hypokalemia and hyperglycemia (Table 2). SSTR scintigraphy was performed while awaiting IPSS. The sizes of the pituitary and lung tumors did not change over two years (Fig. 1B, C, E), and their tumors did not take up Indium-111 (^{111}In)-pentetreotide, a somatostatin analog (Fig. 1F). The somatostatin receptor 2 (SSTR2) agonist octreotide suppressed ACTH levels slightly but not sufficiently (Table 4). Before IPSS, her ACTH and cortisol levels decreased again.

Three months after the second trough phase, she showed recurrence of hyperglycemia and hypokalemia, with elevated ACTH and cortisol levels (Table 2). We had prepared for IPSS in advance and immediately performed it. The ratio of the central to peripheral ACTH levels (1.28) after the CRH (100 μg) load suggested that the responsible tumor was an extra-pituitary lesion (Table 2). At this point, we were still not fully convinced that the lung tumor was responsible for the ACTH production. A previous report suggested that if SSTR scintigraphy failed to localize NETs despite CT showing a tumor, FDG-PET might be helpful for locating the responsible tumor (5). FDG-PET was thus performed, showing a significant tracer uptake in the lung tumor with a maximal standardized uptake value (SUV) of 3.6 in delayed images (Fig. 1G). Based on these findings, we diagnosed her with a lung tumor exhibiting cyclic ACTH production.

After the three-month active phase, lobectomy of the right lung was performed (Fig. 2A). Immunohistochemical analyses showed that tumor cells were positive for chromogranin A, synaptophysin, insulinoma-associated protein 1 (INSM1), and ACTH, indicating that the lung tumor was a ACTH-

Table 2. Sequential Changes in the Parameters of ACTH Production in Each Peak and Trough Phase.

Parameters (unit)	1st peak	1st trough	2nd peak	2nd trough	3rd peak	Post operation
ACTH (pg/mL)	240.7	34.5	135.0	40.9	90.2	15.0
Cortisol (μg/dL)	60.2	9.5	44.9	8.6	34.8	6.7
DHEA-S (μg/dL) (normal range; 7-177)	N.D.	N.D.	N.D.	27	125	33
UFC (μg/day)	N.D.	58.5	1255.0	34.8	1490.0	14.5
0.5 mg DST						
ACTH (pg/mL)	195.6	N.D.	125.0	47.9	N.D.	1.8
Cortisol (μg/dL)	72.3	N.D.	29.9	6.8	N.D.	0.5
8 mg DST						
ACTH (pg/mL)	213.0	57.5	113.0	N.D.	N.D.	N.D.
Cortisol (μg/dL)	69.6	13.5	29.2	N.D.	N.D.	N.D.
IPSS						
Central ACTH	N.D.	33.7	N.D.	N.D.	110.0	N.D.
Peripheral ACTH	N.D.	34.5	N.D.	N.D.	85.8	N.D.
K (mEq/L)	2.2	4.2	2.2	4.0	3.9	3.7
HbA1c (%)	10.2	5.5	9.4	7.4	7.9	6.2

ACTH: adrenocorticotropic hormone, DHEA-S: dehydroepiandrosterone sulfate, UFC: urinary free cortisol, DST: dexamethasone suppression test, IPSS: inferior petrosal sinus sampling, K: potassium, N.D.: not determined

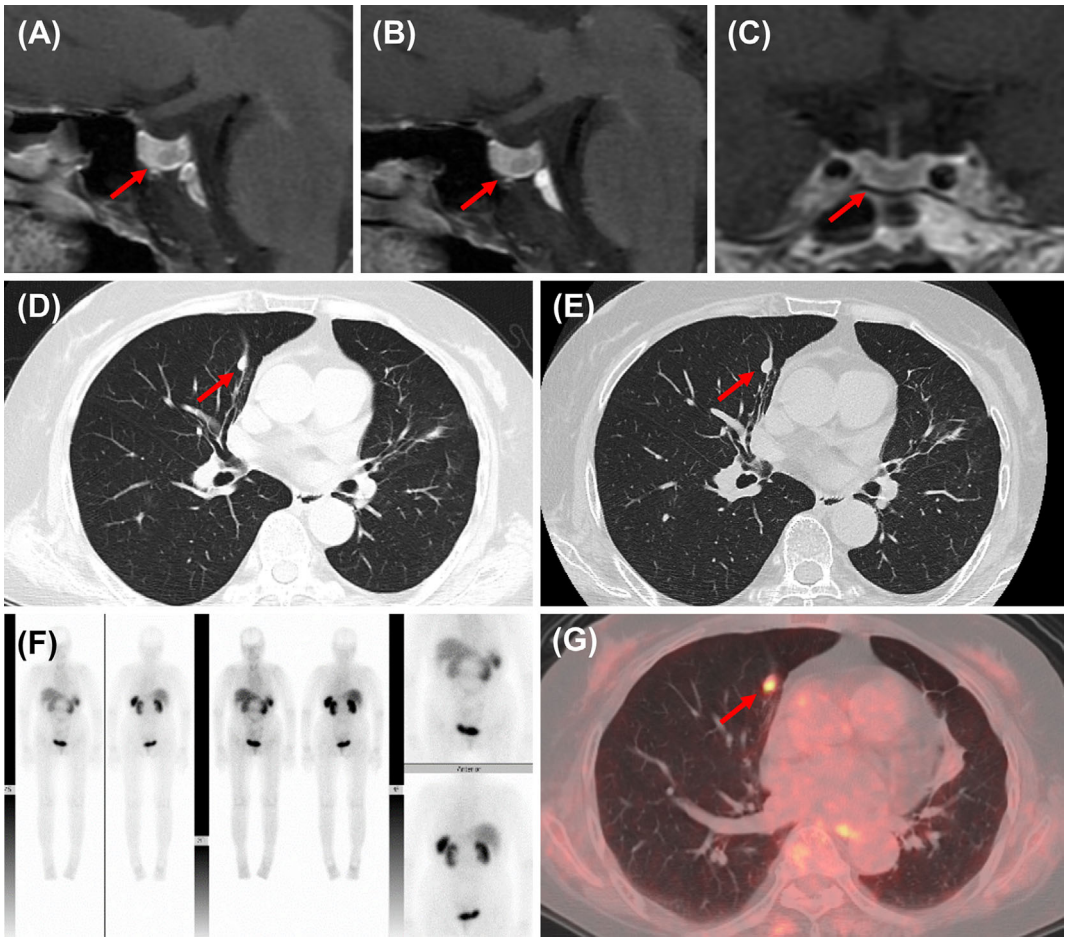

Figure 1. Imaging findings of the patient. T1-weighted contrast-enhanced magnetic resonance imaging (MRI) showing indirect signs of a pituitary nodule (4 mm in diameter) (arrows) in the first peak phase (A) and second peak phase (B, C). Computed tomography showing a nodule (8.8 mm in diameter) in the right lobe of the lung (arrows) in the first peak phase (D) and second peak phase (E). No region showed abnormal uptake of the ^{111}In-pentetreotide (F). Fluorodeoxyglucose positron emission tomography (FDG-PET) showed an increased tracer uptake in the lung tumor (arrow) (G).

Table 3. Changes in the ACTH Levels after 100 μg of CRH Administration.

Parameters (unit)	0 min	30 min	60 min	90 min	120 min
ACTH (pg/mL)	179.5	173.3	185.2	173.8	166.4
Cortisol (μg/dL)	41.2	41.5	44.5	40.1	41.6

Blood samples were collected before or after administration of corticotropin releasing hormone (100 μg).

Table 4. Changes in the ACTH Levels after 50 μg of Octreotide Administration.

Parameters (unit)	0 min	120 min	240 min	360 min
ACTH (pg/mL)	140.0	133.0	86.6	72.3
Cortisol (μg/dL)	47.0	39.6	29.7	24.8

Blood samples were collected before or after administration of octreotide (50 μg).

producing NET (Fig. 2B-E). In addition, the Ki-67 expression was <2% (Fig. 2F). Thus, the tumor was classified as a Grade 1 NET or typical carcinoid, according to the 2021 WHO classification (8). Staining for SSTR2 and SSTR5 was negative (Fig. 2G, H), consistent with the negative uptake of ^{111}In-pentetreotide in the lung tumor. After lobectomy, the ACTH and cortisol levels decreased clearly more than those levels in the past two trough phases and were suppressed by 0.5 mg dexamethasone (Table 2). Her glucose and potassium levels stabilized without any medication. She maintained remission for two years after the surgery.

Discussion

To localize the ectopic ACTH-producing tumor, we should use various whole body-scanning radioisotope imaging modalities, as even if one radioisotope cannot localize ectopic ACTH-producing tumors, other radioisotopes may find them. SSTR scintigraphy is useful for localizing NETs, including ACTH-producing tumors, since most NETs express SSTRs (3). Among the five SSTR subtypes, the type 2 receptor was identified as the most frequently expressed on the surface of NET cells, providing the molecular basis for many clinical applications of somatostatin analogs (1). The ^{111}In-pentetreotide used for SSTR scintigraphy has a high affinity to SSTR2. However, ^{111}In-pentetreotide scintigraphy shows no uptake in NETs with a low SSTR2 expression (9).

FDG-PET is used to identify malignant tumors characterized by their high glucose uptake (4). It can also localize NETs, including ACTH-dependent Cushing's syndrome (5, 10). Although FDG-PET cannot detect autonomous ACTH production and cannot distinguish NETs from other malignant tumors, it detects NETs regardless of their SSTR2 expression. If SSTR scintigraphy fails to localize NETs despite CT showing a tumor, FDG-PET might help find the responsible tumor (5).

Some previous patients with cyclic ectopic ACTH-producing tumors were unable to receive radical resection because their responsible tumors were not identified (6, 7) (Table 5). Therefore, a sequential analysis of these radioisotope imaging modalities is important for the localization of cyclic ectopic ACTH-production tumors and radical resection. In addition to radioisotope imaging, pulmonary artery sampling has been reported as useful in the functional diagnosis of pulmonary nodules in ectopic ACTH-producing tumors (11, 12). It was suggested that this approach should be considered in cases with negative findings on SSTR scintigraphy and FDG-PET. In our case, pulmonary artery sampling might have been performed if the FDG-PET findings had been negative.

Previous reports have suggested that higher grade NETs are less likely to uptake somatostatin analogs than lower grade NETs, and conversely, they are more likely to uptake fluorodeoxyglucose (10, 13). Interestingly, in our case, despite the low Ki-67 index (<2%), the ^{111}In-pentetreotide scintigraphy findings were negative, and the FDG-PET findings were positive. In addition, the maximum standardized uptake value (SUV_{max}) of FDG-PET showed a positive trend with Ki-67 in lung NETs (14). Therefore, we should follow the clinical course of our case carefully, as her radiological findings suggest malignant potential (10).

However, a hypothesis has been proposed that episodic hemorrhaging or synchronic growth and death of ACTH-producing tumor cells may lead to periodic hypercortisolism (15). In addition, lung NETs often show intratumor heterogeneity (8). These insights suggest that temporal and spatial tumor growth and necrosis might cause cyclic ACTH-production and a discrepancy between the Ki-67 index and radiological findings. Since the pathological findings of our case did not indicate necrosis in the observed area, probably due to its heterogeneity, wider observations are needed.

To understand the clinical and laboratory characteristics of patients with cyclic ectopic Cushing's syndrome, we referred to all previous reports since 1999, when FDG-PET started to be used commercially. To this end, we searched a PubMed database (https://pubmed.ncbi.nlm.nih.gov/) using the following keywords 'ACTH,' 'ectopic,' 'cyclic,' 'periodic,' and/or 'intermittent.' Furthermore, we manually checked the reference lists to find relevant articles (6, 7, 16-24). We ultimately found 12 cases of cyclic ectopic Cushing's syndrome (Table 5). Of these 12 cases, the responsible tumor was unable to be localized in 4 cases. Two cases showed negative findings for both ^{111}In-pentetreotide and FDG-PET and received bilateral adrenalectomy. Another two cases did not

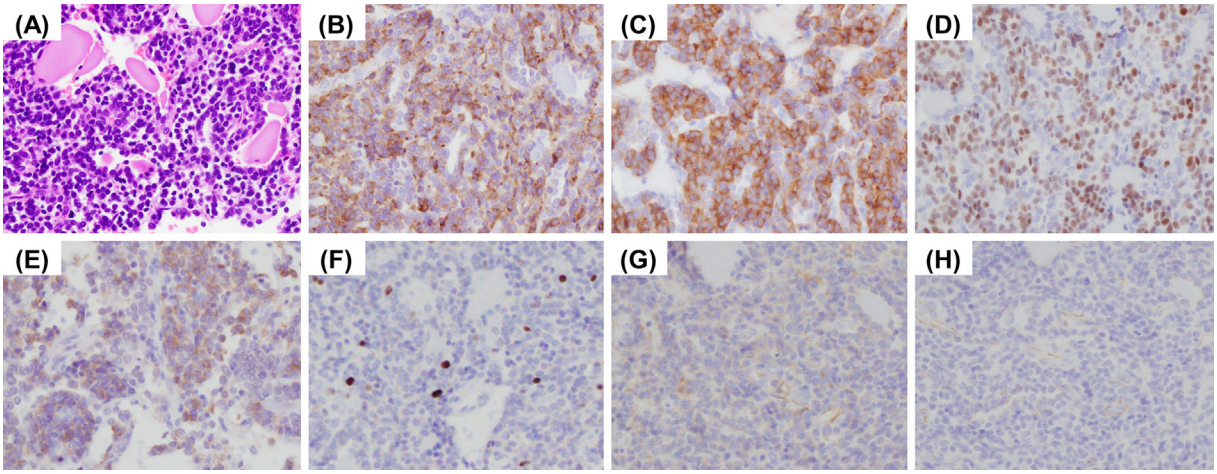

Figure 2. **Histological and immunohistochemical findings of the lung nodule. A microscopic examination of the specimen showed a typical carcinoid tumor (Hematoxylin and Eosin staining) (A). Immunohistochemical staining of the ACTH-producing lung tumor; chromogranin A (B), synaptophysin (C), INSM1 (D), ACTH (E), Ki-67 (F), somatostatin receptor 2 (SSTR2) (G), and somatostatin receptor 5 (SSTR5) (H). The Ki-67 expression was 1.4% (Original magnification of all immunohistochemical images, ×400).**

Table 5. **Summary of the Published Reports of Cyclic Ectopic Cushing's Syndrome.**

Reference	Location	FDG-PET	Scintigraphy	IPSS	Operation	Ki-67 (IHC)	SSTR2 (IHC)	SSTR5 (IHC)	Alternative therapy
(18)	(Unknown)	Negative	Negative	Ectopic	No				Adx, SS analog
(16)	Lung	N.D.	Negative	Ectopic	Yes	<3%	N.D.	N.D.	
(19)	Thymus	N.D.	Positive	Ectopic	Yes	N.D.	N.D.	N.D.	Radiation
(20)	(Unknown)	Negative	Negative	Ectopic	No				KTZ, Adx
(21)	Lung	N.D.	Positive	N.D.	No	N.D.			SS analog
(22)	Carotid glomus	Positive	Positive	Ectopic	Yes	N.D.	N.D.	N.D.	Chemo, KTZ, Adx
(7)	(Unknown)	N.D.	N.D.	Ectopic	No				MTY
(23)	Thymus	N.D.	N.D.	N.D.	N.D.	N.D.			
(23)	Pancreas	N.D.	N.D.	N.D.	N.D.	N.D.			
(24)	Lung	N.D.	N.D.	N.D.	Yes	Low	N.D.	N.D.	
(17)	Pancreas	Negative	Negative	Fail	Yes	<20%	N.D.	N.D.	Adx, Chemo
(6)	(Unknown)	Negative	N.D.	N.D.	No				MTY
This case	Lung	Positive	Negative	Ectopic	Yes	1.4%	Negative	Negative	

PubMed database was searched using the following keywords 'ACTH,' 'ectopic,' 'cyclic,' 'periodic,' and/or 'intermittent,' since 1999 FDG-PET was started to use commercially. All isotope for scintigraphy were ^{111}In-pentetreotide except for the case reported in 2019, it was ^{68}Ga-DOTATATE.

FDG-PET: fluorodeoxyglucose positron emission tomography scan, IPSS: bilateral inferior petrosal sinus sampling, SSTR: somatostatin receptor, IHC: immunohistochemistry, Adx: adrenalectomy, SS analog: somatostatin analog, KTZ: ketoconazole, MTY: metyrapone, Chemo: chemotherapy, N.D.: not determined

complete scintigraphy or FDG-PET and were administered metyrapone, which reduces cortisol production in the adrenal glands. Of the 12 cases, the SSTR expression was analyzed in only one case. This case was negative on SSTR scintigraphy but revealed an elevated mRNA expression of SSTR2 in the resected tumor. Three cases included mention of the Ki-67 index. One of the three cases had a high expression of Ki-67 and metastasized after the operation. The prognosis was unknown in the other two cases. This review of the literature suggests that localizing the responsible tumors for radical resection is difficult without both SSTR scintigraphy and FDG-PET. In addition, cyclic ACTH-producing tumors may not show a correlation between the FDG uptake and NET grade. Our case is the first to include assessments of both radioisotope imaging findings and the SSTR2 and 5 expression by immunohistochemistry. The further accumulation of patients with data on imaging findings and histological examinations will be required to better understand the heterogeneous nature of cyclic ectopic ACTH-producing tumors.

In ectopic ACTH-producing tumors, the diagnosis and localization are often challenging, especially if the tumor shows cyclic secretion. As previously reported, functional tests and localization, such as DST and IPSS, should be per-

formed during the active phase of cyclic ACTH production (16, 17). However, the findings of these tests may be "false negative" if the proper phase is missed. We must therefore anticipate the active phase according to specific parameters. In the present case, blood glucose levels, blood pressure, and serum potassium levels were used as biomarkers to anticipate the beginning of the active phase. Physical and laboratory findings should be checked carefully to identify the active phase and diagnose cyclic ACTH production.

We can speculate the efficacy of somatostatin analogs for ACTH-dependent Cushing's syndrome with a suppression test of ACTH secretion after somatostatin analog administration (25). In our case, the SSTR2 agonist octreotide suppressed ACTH levels partially but not sufficiently (Table 4), suggesting that the responsible tumor expresses SSTR2 rarely, which is consistent with the histological findings. We speculate that her lung NET did not take up ^{111}In-pentereotide due to the low SSTR2 expression and small size.

Conclusion

A sequential assessment using subsequent FDG-PET is recommended if SSTR scintigraphy is negative. The SSTR-negative immunohistochemical findings support negative SSTR scintigraphy. In addition, positive FDG-PET findings and a low Ki-67 index may suggest malignant potential or intratumor heterogeneity in lung NETs exhibiting cyclic Cushing's syndrome.

Written informed consent was obtained from the patient.

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

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