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Case Report

An ACTH-Producing Neuroendocrine Tumor: Clinical Course of Multidisciplinary Therapy Including Peptide Receptor Radionuclide Therapy – A Case Report

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Abstract
Introduction: Clinical experiences of peptide receptor radionuclide therapy (PRRT) in patients with adrenocorticotropic hormone (ACTH) producing neuroendocrine tumor (NET) were extremely rare. ***Case Presentation:*** A 60-year-old woman with hypertension, lower-extremity edema, hypoalbuminemia, hypokalemia, and multiple hepatic tumors was hospitalized for further examination and treatment. Endocrine testing detected excessive levels of ACTH and cortisol in her blood. Pathohistological examination revealed the hepatic lesions to be ACTH-positive grade 2 NETs (G2). A diagnosis of ectopic ACTH-producing NET was made. The patient was initially treated with the 11-hydroxylase inhibitor, metyrapone, to control hypercortisolemia and the long-acting somatostatin analog, lanreotide. Simultaneously, everolimus was continued for about 1 year. Subsequently, hepatic tumors were surgically resected, leading to successful and rapid normalization of ACTH secretion and resolution of hypercortisolemia. However, the disease relapsed and presented with multiple hepatic masses and increased ACTH 18 months after surgery. As sunitinib and subsequent streptozocin chemotherapy failed to control the

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disease, PRRT with ^{177}Lu-DOTATATE was performed. ACTH levels increased after initiation of PRRT, and clinical manifestations, such as pigmentation, hypertension, and hyperglycemia, were remarkable. The patient was treated with antihypertensive and antidiabetic agents, and required an increased dose of metyrapone and addition of the cortisol biosynthesis inhibitor, osilodrostat. After four cycles of PRRT, the hepatic tumors showed a remarkable reduction in size with normalization of ACTH level and withdrawal of cortisol synthesis inhibitors. ***Conclusion:*** Although PRRT was effective, we should consider the occurrence of hormonal crisis during the therapy. Due to the rarity and complexity of hormone-producing tumors, cooperation between medical oncologists and endocrinologists is important for patient management.

Introduction

Neuroendocrine neoplasms are comparatively rare tumors with an estimated age-adjusted incidence of 6.98 per 100,000 in the USA [1]. In Japan, the estimated prevalence of gastroenteropancreatic neuroendocrine neoplasms was 3.54 per 100,000 based on the national cancer registry in 2016 [2]. Among them, neuroendocrine tumors (NETs) show indolent well-differentiated types [3] and arise in various organ systems, including the pancreas, gastrointestinal tract, lung, and mediastinum [4, 5]. NETs often metastasize to the liver [4]), but primary hepatic NET has also been reported [5–8]. In addition, some tumors are functional, leading to paraneoplastic endocrine syndromes due to tumor-produced and/or ectopic oversecretion of hormones and vasoactive substances [6, 7, 9–14]. Cushing's syndrome (CS), characterized by excessive secretion of adrenocorticotropic hormone (ACTH) or corticotropin-releasing hormone, is one of the best-known NET-related paraneoplastic endocrine syndromes [10–14].

Here, we report the clinical course of multimodal therapy including somatostatin analogs, molecular targeted agents, surgery, and peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE in a case of ACTH-producing NET treated with serial intensive therapies. PRRT was effective for radiological tumor reduction and resulted in successful control of ACTH secretion.

Case Report

A 60-year-old woman, without any relevant medical history, was admitted to a local hospital in August 2017 because of hypertension, lower-extremity edema, and increased body weight (5 kg) over the past 2 weeks. Multiple liver masses were detected on ultrasonography and the patient was referred to our hospital for further examination. The patient was 159.5 cm in height with a body weight of 58 kg. Blood pressure was 172/93 mm Hg and bilateral lower-extremity pitting edema was evident, but hallmark symptoms of CS, such as moon face and pigmentation, were absent. Laboratory findings are summarized in Table 1. Blood tests showed increased white blood cell count, serum alanine aminotransferase, random plasma blood glucose (320 mg/day), hemoglobin A1c (8.2%), brain natriuretic peptide (61.5 pg/mL, normal; <18) level, and decreased serum potassium (2.2 mEq/L) level. Endocrinological assessment of blood samples drawn on waking early in the morning after 30 min of bed rest, revealed marked secretion of plasma cortisol (59.2 μg/dL, normal;

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Table 1. Laboratory data on admission

Hematology		
WBC	11,180	/μL
Neu	89.8	%
Lym	6.6	%
RBC	416	$\times 10^4$/μL
Hb	13.2	g/dL
PLT	13.7	$\times 10^4$/μL
Biochemistry		
TP	5.7	g/dL
Alb	3.4	g/dL
AST	28	U/L
ALT	77	U/L
γGTP	188	U/L
T-bil	0.95	mg/dL
ALP	242	U/L
LD	390	U/L
CK	247	U/L
AMY	55	U/L
CHE	169	U/L
TC	180	mg/dL
TG	99	mg/dL
HDL-C	82	mg/dL
LDL-C	73	mg/dL
BUN	22.3	mg/dL
Cre	0.49	mg/dL
UA	2.6	mg/dL
Na	143	mEq/L
K	2.2	mEq/L
Cl	95	mEq/L
CRP	0.07	mg/dL
BS	320	mg/dL
HbA1c	8.2	%
BNP	61.5	pg/mL
Endocrinological data		
TSH	0.167	μIU/mL
FT3	1.28	pg/mL
FT4	1.29	ng/mL
ACTH	817	pg/mL
Cortisol	59.2	μg/dL
Glucagon	223	pg/mL
Gastrin	1,490	pg/mL
IRI	17.7	μU/mL
CPR	1.99	ng/mL

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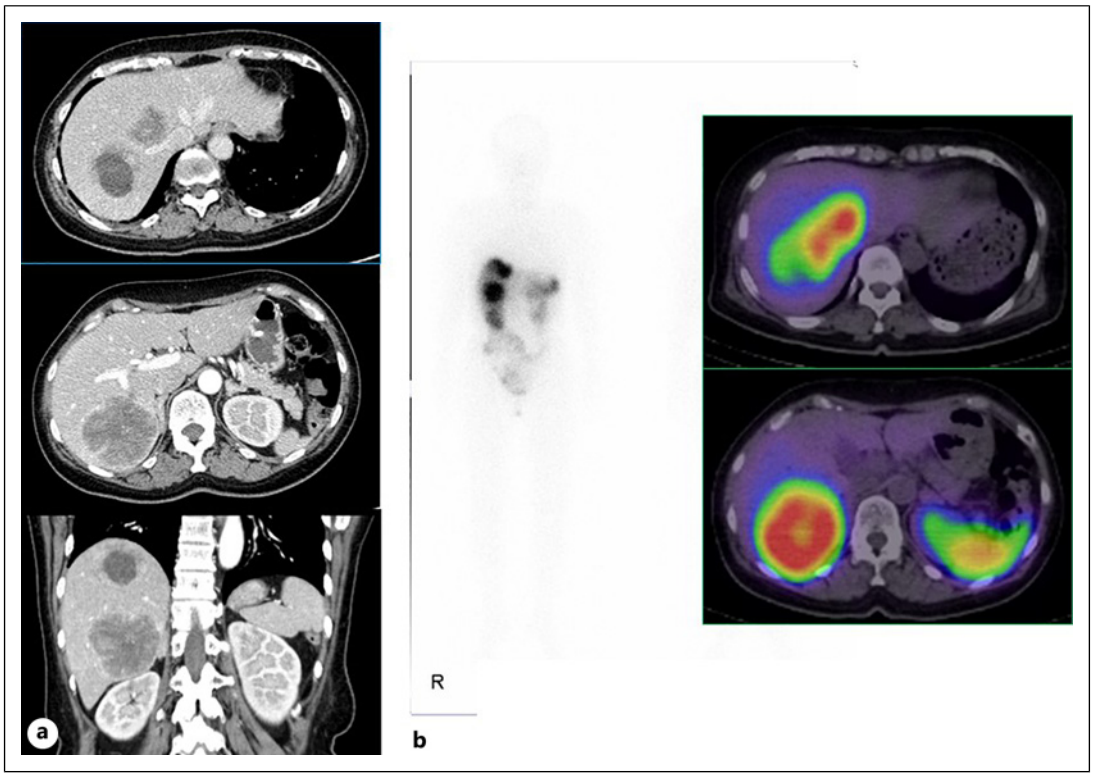

Fig. 1. Radiographic findings on diagnosis. **a** Abdominal enhanced computed tomography detected hepatic masses with almost identical patterns of heterogeneous enhancement at the time of admission. **b** These hepatic lesions were positive on somatostatin receptor scintigraphy using ^{111}indium-labeled pentetreotide.

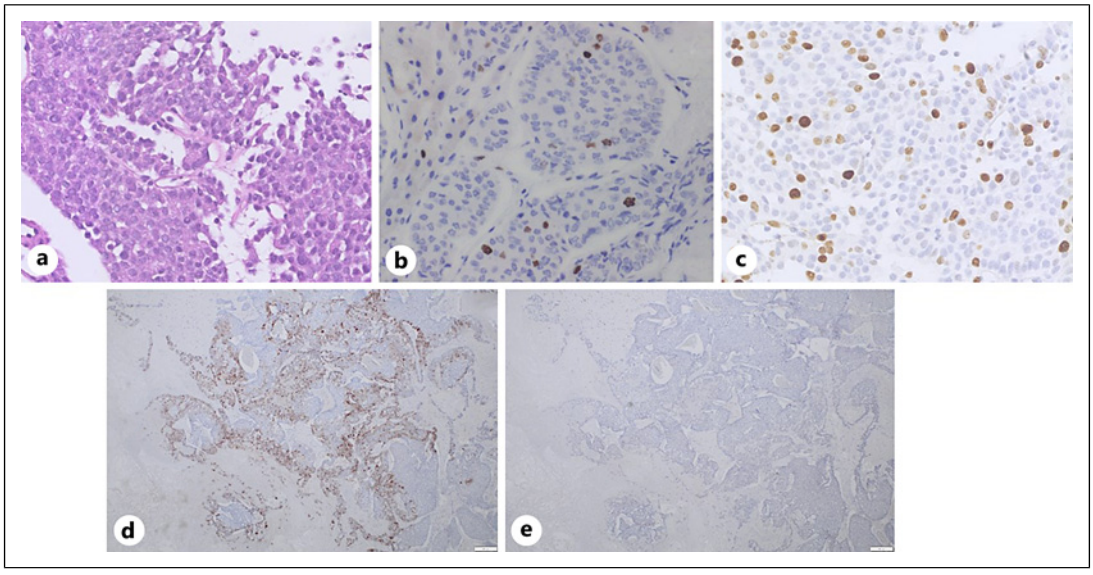

Fig. 2. Pathological findings of the liver tumors. **a** Well-differentiated tumor cells were observed in biopsy specimens (hematoxylin and eosin staining. **b** Nuclear Ki-67 expression was positive in 7.5% of the tumor cells. The tumor cells were positive for chromogranin A (**c**) and ACTH (**d**) and negative for corticotropin-releasing hormone (**e**) (magnification: ×4).

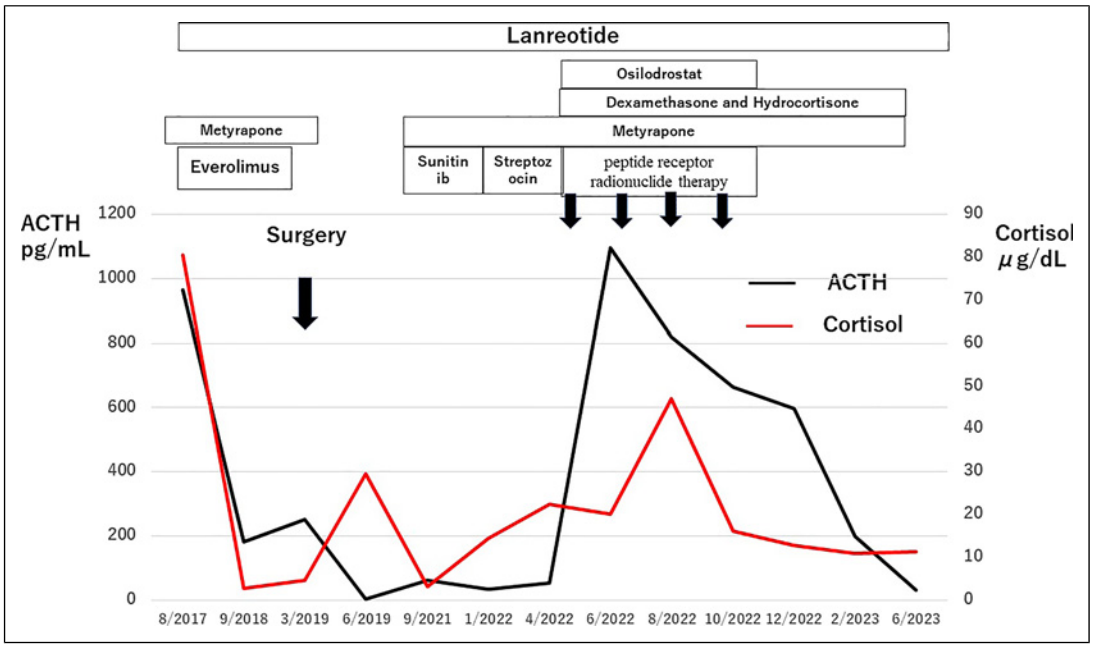

Fig. 3. Treatments and time courses of ACTH and cortisol secretion in the present case. Black arrow: hepatic lobectomy. Black arrows: peptide receptor radionuclide therapy.

7.1–19.6) and ACTH (817 pg/mL, normal; 7.2–63.3). There were no abnormalities in tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19–9, α-fetoprotein, carbohydrate antigen 125, or soluble interleukin-2 receptor. Whole-body computed tomography (CT) showed at least three right hepatic masses with almost identical patterns of heterogeneous enhancement (Fig. 1a). ^{111}Indium-labeled pentetreotide scintigraphy showed radioligand accumulation in the intrahepatic tumors, and no other lesions were detected (Fig. 1b). Upper and lower gastrointestinal endoscopy revealed no abnormal findings. Histopathological immunohistochemical analysis of a percutaneous liver biopsy specimen showed diffuse expression of chromogranin A and ACTH (DAKO clone 02A3) in the tumor cells, with a Ki-67 index of 7.5% (Fig. 2). The tumor cells were negative for corticotropin-releasing hormone (10944-1-AP; Proteintech) (Fig. 2e). Re-examination showed further increases in plasma ACTH (964.3 pg/mL) and cortisol (80.4 μg/dL). Although dynamic endocrinological examinations were not performed and the primary site remained unknown, the patient was diagnosed with ACTH-producing NET (G2 according to the 2019 World Health Organization classification of pancreatic NEN), with extensive liver involvement.

Potassium supplementation (potassium chloride, 1,800–3,600 mg/day) was begun, and the potent 11β-hydroxylase inhibitor, metyrapone, was administered and increased to a dose of 2,550 mg/day, which ameliorated the cortisol-related symptoms. The patient was treated with long-acting somatostatin analog (lanreotide, 120 mg/month) and an mTOR-inhibitor (everolimus, 10 mg/day). Treatment and hormonal changes in the present case are shown in Figure 3. The hepatic tumors diminished in size temporarily after the initiation of lanreotide and everolimus therapy, and remained stable for over 1 year. During this period, ACTH level was still high, although cortisol was controlled to within the normal range by treatment with 1,500–2,000 mg per day of metyrapone. With the patient's consent, we performed surgery to remove the tumors, consisting of partial left hepatic lobectomy plus percutaneous transhepatic portal vein embolization followed by right hepatic lobectomy 2 weeks later. This strategy led to rapid normalization of ACTH and subsequent resolution of hypercortisolemia.

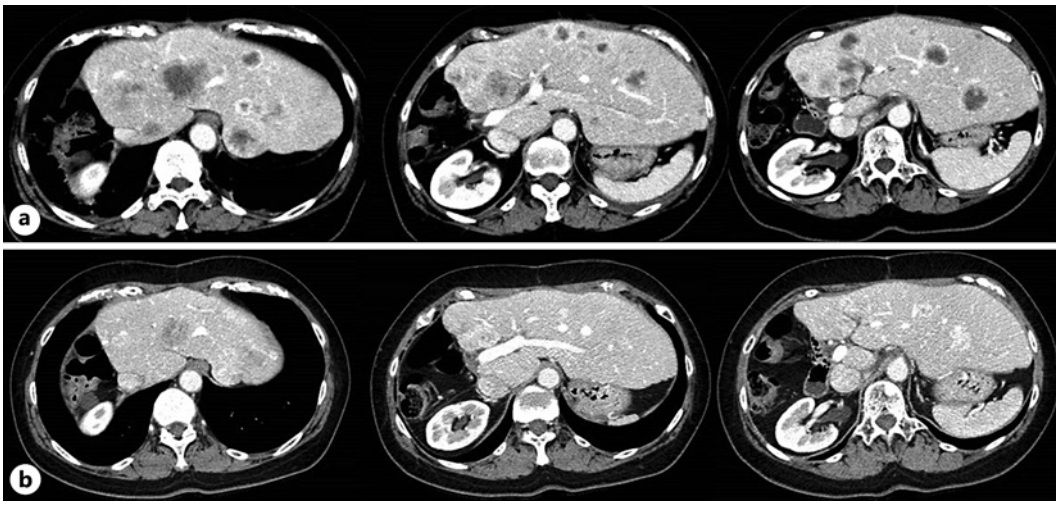

Fig. 4. Hepatic masses on abdominal enhanced computed tomography before (**a**) and 14 months after (**b**) the initiation of PRRT.

However, multiple hepatic metastases developed 18 months after surgery, and ACTH increased again, consistent with recurrence. Sunitinib (multitargeted receptor tyrosine kinase inhibitor, 25–37.5 mg/day) for 3 months and subsequent streptozocin therapy (1,000 mg/m^2 IV weekly) for 3 months failed to control the hepatic lesions and excess secretion of ACTH. Then, PRRT with ^{177}Lu-DOTATATE (7.4 GBq) was performed. ACTH levels increased after initiation of PRRT and clinical manifestations of CS, including pigmentation, hypertension (systemic pressure >150 mm Hg), hyperglycemia (>300 mg/dL), and increased body weight (2 kg/month), were observed. The patient was treated with antihypertensive and antidiabetic agents and required an increase in dose of metyrapone. The dose of metyrapone was increased (maximum dose 3,000 mg/day) and combined with both adrenal 11β-hydroxylase and aldosterone synthase inhibitor (osilodrostat phosphate, 2–4 mg/day). Dexamethasone (0.5–1.0 mg/day) and hydrocortisone (10–20 mg/day) were administered to avoid adrenal insufficiency. However, ACTH decreased during serial cycles of PRRT and consequently normalized 1 year after initiation of PRRT. Along with the decrease in ACTH, the doses of steroidogenesis inhibitors and potassium chloride were gradually reduced and successfully withdrawn 18 months after the start of PRRT, as well as cessation of antihypertensive and antidiabetic agents. Serial treatments and time courses of ACTH and cortisol secretion in the present case are summarized in Figure 3. Contrast-enhanced CT showed a marked reduction in the size of hepatic masses 6 months after cessation of 4 cycles of PRRT (Fig. 4). Treatment with long-acting somatostatin analog was continued throughout the clinical course in the present case, including after PRRT therapy.

Discussion

We presented a case of ACTH-producing NET mainly involving the liver treated with multiple therapeutic modalities. Although several cases of primary hepatic NET have been reported [5–8], the diagnosis and identification of primary hepatic NET are difficult. NETs, particularly gastroenteropancreatic NETs, frequently develop liver metastasis [4] and even small primary NETs can give rise to large hepatic metastases [15, 16]. Indeed, it remained unknown whether hepatic masses represented primary or metastatic disease in the present

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case; however, we could not detect an extrahepatic primary site throughout the clinical course.

Our case exhibited ACTH-producing features, which is also extremely rare. Several previous case reports indicated the development of ectopic CS after radiographic progression of NET following diagnosis [10, 11]. However, the initial and rapidly progressing CS-related clinical symptoms in the present case were unique, leading to the detection of hepatic tumors. Therefore, this case provided insight into clinical manifestations of ectopic CS in patients with NETs.

Various therapeutic modalities are available for treating inoperable and metastatic NETs [17–20]. PRRT has been available since September 2021 in Japan and was more effective for disease and hormonal control than targeted agents and chemotherapy in the present case. Indeed, the response rate and progression-free survival time in a clinical trial of PRRT [14] were superior to those of molecular targeted therapies [19, 20]. These data and our experience suggested a strong role of PRRT in tumor reduction in patients with NETs. In general, ectopic CS patients without complete resection have a poorer prognosis [10, 11] compared with those in cases of nonfunctional NETs. Therefore, we suggest that PRRT should be performed preferentially in the course of treatment in cases with ACTH-producing NET.

PRRT has been shown to be useful for control of symptoms in refractory carcinoid syndrome, but carcinoid and/or hormonal crisis are known complications of PRRT in cases of functional NET [21–25]. In the present case, ACTH levels increased after initiation of PRRT and required intensive treatment with cortisol inhibitors. This increase was likely due to oncolysis of ACTH-producing tumor cells by PRRT. We speculated that tumor volumes and/or the efficacy of PRRT could affect the development of hormonal crisis. Thus, increased hepatic volume in the present case might be a major risk factor for the hormonal crisis, but we emphasized that acute exacerbation of clinical manifestations due to hormonal crisis by oncolysis should be considered after any treatment in cases of functional NETs.

Regarding the adverse events in PRRT, nausea, hematotoxicity, and renal toxicity during PRRT have been reported [17, 18, 23–25], but there were no gastrointestinal toxicities and abnormalities in laboratory findings including hematology and creatine in our case. Thus, scheduled PRRT every 8 weeks could be performed, while the patient had been monitored carefully, including measurements of plasma cortisol, potassium, and glucose levels, and blood pressure, and was managed intensively with steroidogenesis inhibitors. Consequently, the dose of cortisol inhibitor and/or glucocorticoid replacement therapy could be reduced with careful monitoring of symptoms and cortisol secretion. The development of adrenal insufficiency is a major concern with excessive cortisol inhibitor dose [9], although it did not occur in the present case. Thus, cooperation between medical oncologists and endocrinologists is important for the management of patients with functional NET.

In conclusion, we reported the clinical course of multidisciplinary therapy in an ACTH-producing NET. Late-line therapy by PRRT was effective, but the patient developed hormonal crisis and required intensive medical treatment for hypercortisolemia. The possibility of hormonal crisis during therapy should be considered in the treatment of functional NETs.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543177).

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Author Contributions

T.K., A.S., K.K., and S.K. contributed to medical therapy, patient follow-up, data collection, and writing the manuscript. M.Y. and M.K. contributed to data collection and data analysis. T.N. performed surgeries. Y.S., S.K., and M.I. contributed to data collection of pathological findings. T.U. performed peptide receptor radionuclide therapy. T.K. is the corresponding author. All authors contributed to the article and approved the submitted version.

Data Availability Statement

All data generated or analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.

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