# Von Hippel Lindau disease with metastatic pancreatic neuroendocrine tumor causing ectopic Cushing's syndrome

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C A S E   R E P O R T

## Abstract

We present a 39-year-old woman who was previously diagnosed with Von Hippel Lindau Disease (VHLD). She had surgery and radiotherapy for cranial hemangio-blastoma (HA) 11 years ago and had unilateral adrenalectomy for pheochromocy-toma in another hospital 6 month prior to her admission to our center. Moon face, buffalo hump, central obesity, progressive weight gain and menstrual irregularities persisted after adrenalectomy. Her laboratory results were consistent with ectopic Cushing's syndrome (ECS). A pancreatic solid mass with a nodule on the left lung were revealed upon computed tomography. In addition, Gallium-68 Somatostatin Receptor PET confirmed the pancreatic involvement and demonstrated additional lesions on the left lung and in the aortocaval lymphatic system on the right side, suggesting metastatic pancreatic neuroendocrine tumor (PNET). Peptide receptor radionuclide therapy (PRRT) with [$^{177}$Lutetium-DOTA$^0$,Tyr$^3$] octreotate was performed on the patient, with no side effects observed. She was discharged from the hospital 10 days after the first cycle.

**Abbreviations:**
VHLD    - Von Hippel Lindau disease
HA      - Hemangioblastoma
PNET    - Pancreatic neuroendocrine tumors
ECS     - Ectopic Cushing's syndrome
SRTRT   - Somatostatin receptor-targeted radionuclide therapy
CS      - Cushing's syndrome
PRRT    - Peptide receptor radionuclide therapy

## INTRODUCTION

Von Hippel Lindau Disease (VHLD) is an autosomal dominant disease characterized by presence of hemangioblastoma (HA) in the central nervous system, retinal hemangioblastoma, renal cell carcinoma, renal cysts, pancreatic cystadenomas and pancreatic neuroendocrine tumors (PNET).

Pancreatic lesions in VHLD are commonly benign cystadenomas. Occasionally, neuroendocrine tumors of the pancreas accompany VHLD and when they are present these lesions are usually nonfunctional, slow growing and have a low rate of metastasis (Hes *et al.* 1999; Hammel *et al.* 2000; Marcos *et al.* 2002). Although surgery is the first option for treatment, new treatment modalities have emerged, especially for inoperable tumors. Herein, we present a rare case of VHLD with metastatic, ectopic Cushing's syndrome (ECS) causing PNET for which somatostatin receptor-targeted radionuclide therapy (SRTRT) was administered.

## CASE

A 39-year-old woman presented with progressive weight gain of 40 kg in 5 years and menstrual irregularities in the previous 10 month. Her medical history was notable for VHLD, which was diagnosed 6 month earlier with the presence of cranial HA, pheochromocytoma, and renal and pancreatic cysts. Her father and sister were also known to have cranial HA but neither was diagnosed with VHLD. The patient had surgery and radiotherapy for HA 11 years earlier. She had unilateral adrenalectomy for pheochromocytoma in another hospital 6 month before her admission to our center. She did not smoke, drink alcohol or use illicit drugs. She was referred to our center from another hospital because her laboratory test results were consistent with Cushing's syndrome (CS) and her cushingoid features persisted after adrenalectomy.

On physical examination, she was afebrile; her pulse was 78 beats per minute, blood pressure 110/80 mmHg, weight 87 kg and height 150 cm. She had moon face, buffalo hump and central obesity. The examination of the skin did not reveal striae but there were lesions consistent with pitriasis versicolor on her trunk and acanthosis nigricans in axillary regions. Her initial laboratory results are shown in Table 1. The two screening tests pointed out the presence of CS: the urinary-free cortisol level was above 1 000 nmol per 24 hours and the cortisol level after 1 mg dexamethasone overnight test was 21 µg/dl. For diagnosis of CS, the 2-day 2 mg test was performed and again showed a nonsupressed cortisol level of 19.4 µg/dl. The result of the 8 mg overnight test was 36.3 µg/dl which, together with absence of an adenoma in sella MRI, excluded a pituitary source. Basal ACTH levels with nonsupressed DHEA-SO4 level (264.2 µg/dl) led to the suspicion the hypercortisolism did not have an adrenal source, but rather was the result of ectopic ACTH secretion. Meanwhile, as the patient's

**Tab. 1.** Laboratory test results.

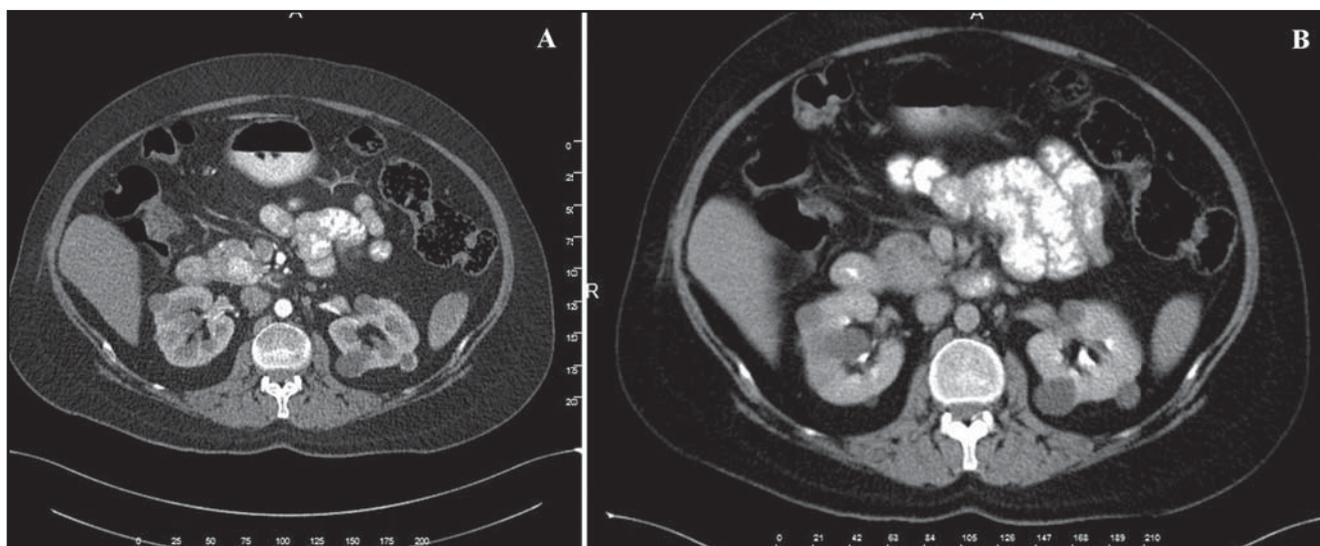| Variable | Result | Reference Range |
|---|---|---|
| Cortisol (µg/dl) | 18.9 | 5–23 |
| ACTH (pg/ml) | 68.40 | 0–46 |
| 24-Hour Urine Collection | | |
| Valinemandelic acid (mg/24 hr) | 0.54 | 1.4–6.6 |
| Homovalinic acid (µg/24 hr) | 4.07 | 2–6.9 |
| Metanephrine (µg/24 hr) | 131.67 | 105–354 |
| Normetanephrine (µg/24 hr) | 94.61 | 74–297 |



**Fig. 1.** Arterial (A) and venous (B) phases of abdominal CT showing pancreatic lesion with venous washout

hypercortisolim progressed, treatment with ketaconazole 600 mg/day was initiated.

The initial workup for detection of an ectopic source included thorax and abdominal CT, which revealed a 13-mm noncalcified nodule in the inferior lobe of the left lung and, in addition to numerous pancreatic cysts, 3 lesions of 1.8 cm in the uncinate process, 8 mm at the posteromedial of the first lesion and 12 mm at conjuncion of the collum and corpus of the pancreas, all of which showed rapid contrast enhancement in arterial phases (Figure 1). Octreotid scintigraphy confirmed the presence of a lesion with somatostatin receptor in the left lung and an additional lesion in the neighbourhood of the anterior region of the right kidney. Gallium-68 Somatostatin Receptor PET revealed a primary tumor with intense somatostatin type-2 receptor involvement in the pancreatic head together with metastatic lesions in the aortocaval lymphatic system at the level of the right kidney hilus and in the posterior segment of the left lung inferior lobe (Figure 2). With endoscopic ultrasonography, a fine needle aspiration biopsy of the lesion on the pancreatic head was performed. The cytologic and immunocytochemical findings were consistent with a low-grade neuroendocrine tumor (synaptophysin and chromogranin were strongly positive, CD56 was focal membranous positive and Ki-67 index

was below 1%). Because the tumor was widely metastatic, surgery was not thought to be the first choice. Instead, peptide receptor radionuclide therapy (PRRT) with [$^{177}$Lutetium-DOTA$^0$,Tyr$^3$] octreotate for a total of 4 cycles, once every 6–8 weeks, was planned. She did not experience any side-effects and was discharged from the hospital 10 days after the first cycle (Figure 3). During her follow-up, 2 months after the discharge, her medical condition was stable and the urinary-free cortisol excretion was still high (2519 nmol per 24 hours).

## DISCUSSION

In this report, we present a Von Hippel Lindau Disease case with ectopic Cushing's syndrome. To our knowledge, there is no reported case in the literature of VHLD presenting with ECS caused by widely metastatic pancreatic neuroendocrine tumor and treated with peptide receptor radionuclide therapy.

Pancreatic neuroendocrine tumor is a rare presentation of pancreatic involvement in VHLD, with a prevalence of 6–17% (Binkovitz *et al.* 1990; Libutti *et al.* 1998; Marcos *et al.* 2002; Blansfield *et al.* 2007; Vinik *et al.* 2011). Detection of PNET in cases of VHLD requires a high index of suspicion. Absence of optimal standards for screening these tumors in VHLD make
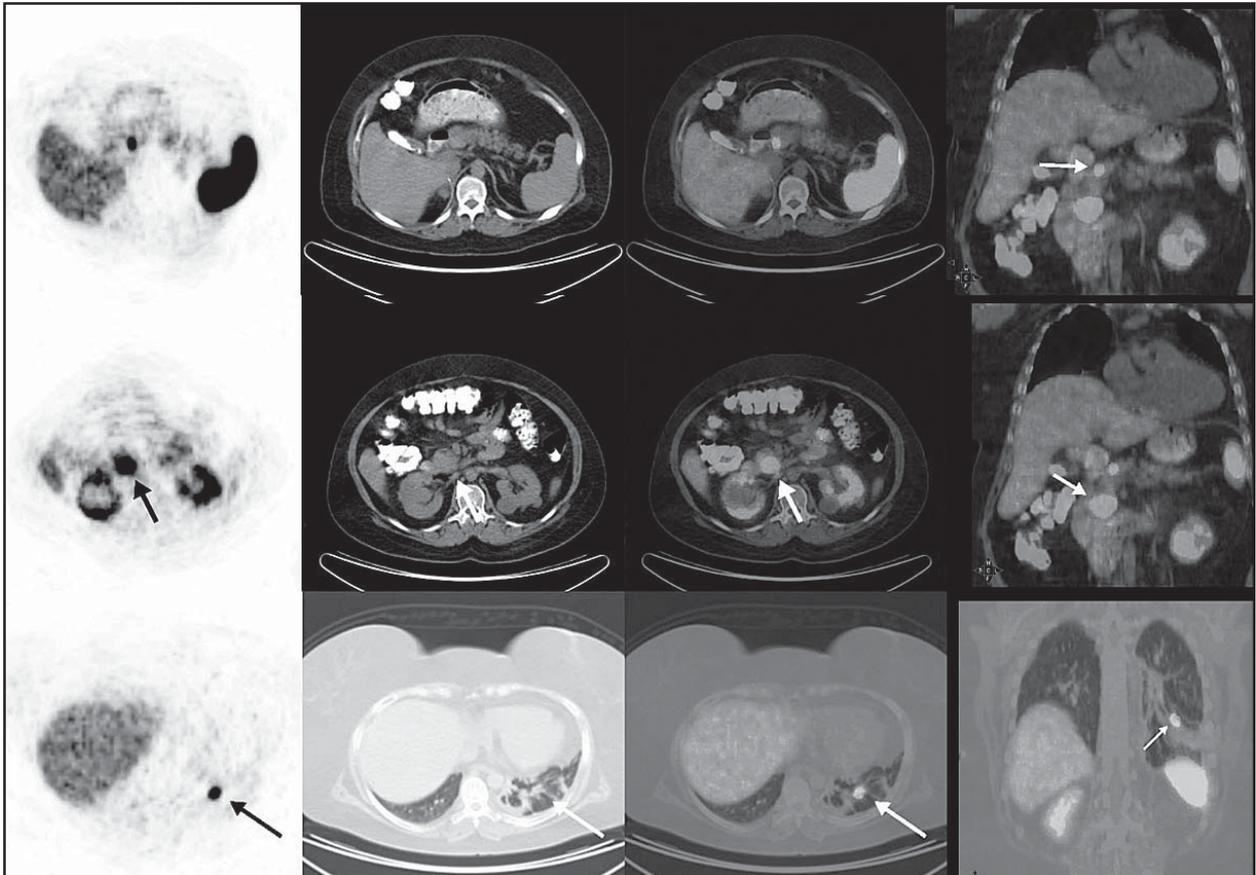


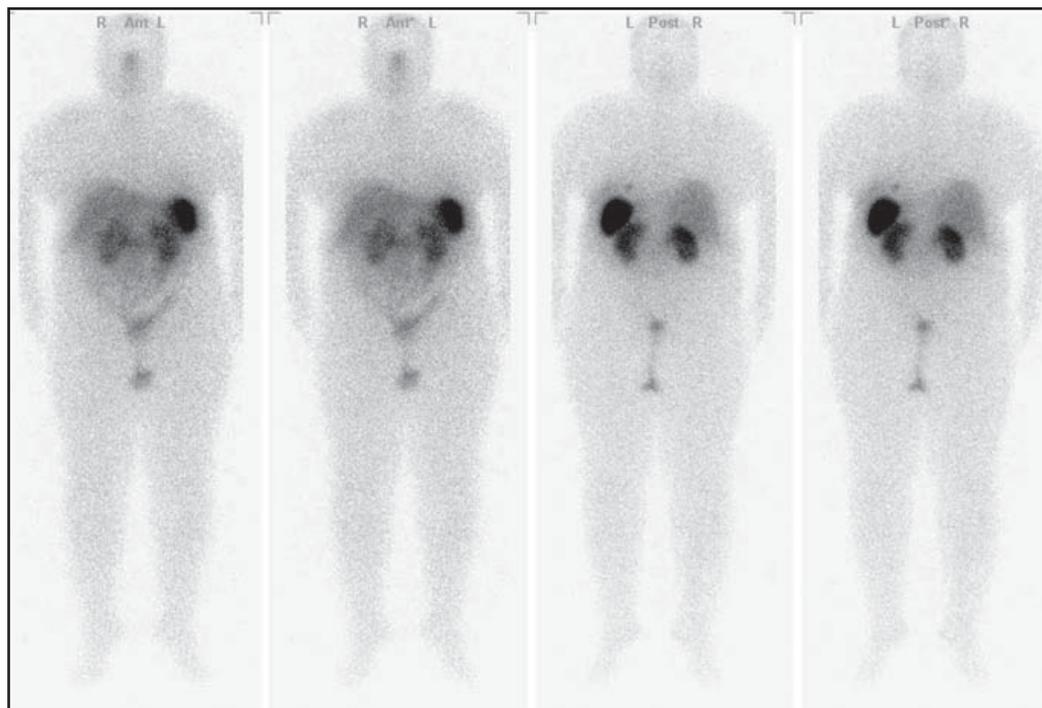**Fig. 2.** Gallium-68 Somatostatin Receptor PET showing primary tumor and its metastases

**Fig. 3.** Whole body scan after the third day of PRRT

it more difficult to recognize their presence. However, awareness of their characteristics will ease the problem of late diagnosis. PNETs are highly vascular tumors, which cause enhancement in early arterial phases, both in CT and MR imaging, with 52% of them located in the pancreatic head (Marcos *et al.* 2002). When they are present in VHLD, PNETs are usually indolent and no more than 10% of these tumors metastasize. This is in contrast to sporadic ones, which have a higher rate of metastasis, mortality and morbidity (Marcos *et al.* 2002). PNETs commoly metastasize to the liver. The presented case is an exception since the liver was free of metastasis despite the involvement of the lung and aortacaval lymphatic system.

PNETs are usually asymptomatic because are usually not hormonally hyperfunctional (Hes *et al.* 1999; Hammel *et al.* 2000). ECS is an extraordinary situation for this silent endocrinological nature of PNETs. These tumors are the source of ectopic ACTH secretion in up to 16% of the cases (Wajchenberg *et al.* 1994; Amikura *et al.* 1995; Orth, 1995; Zhu *et al.* 1996; Boscaro *et al.* 2001; Oberg *et al.* 2002). Pheochromocytomas, one of the components of VHLD, can also be the source of ectopic ACTH secretion. In this case, normal values of urinary metanephrines excluded this possibility. Presence of typical cushingoid features such as central obesity, moon face, buffalo hump and pleathore instead of the more characteristic presentation of ECS, with hypokalemia, muscle weakness and weight loss, denoted the chronic course of ECS.

The mainstay of management in cases with PNETs is surgery. However, treatment should be individualized based on both the characteristics of the patient and the tumor. In case of metastatic PNETs, new therapeutic approaches include SRTRT. In the presented case, widespread metastasis rendered the tumor inoperable; therefore, PRRT with [$^{177}$Lutetium-DOTA$^0$,Tyr$^3$] octreotate was planned for its management. $^{177}$Lutetium-labeled somatostatin analog has a highly specific capacity to bind to the somatostatin receptor on the tumor cells and radioactivity is retained in the tumor cells for a sufficient time despite the relatively rapid clearance of residual radioactivity (Kwekkeboom *et al.* 2011). Correspondingly, it has a greater effect on tumor cell level with fewer systemic side-effects. All of these factors make PRRT preferred to external beam irradiation or systemic chemotherapy (Kwekkeboom *et al.* 2011).

In conclusion, timely diagnosis of PNETs in VHLD is of clinical importance. Although they are notorious for being indolent, they may have a wide spectrum of hormonal activity and may be diagnosed when they are metastatic. So accurate diagnosis warrants a high index of suspicion and a multidisciplinary approach. Treatment should be individualized with options of novel therapeutic approaches.

## ACKNOWLEDGMENTS

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