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Case report

Pulmonary arterial sampling was useful for localizing ectopic ACTH production in a patient with bronchial carcinoid causing Cushing syndrome

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ABSTRACT

OBJECTIVE: We report a 44-year old man with ectopic adrenocorticotropic hormone (ACTH) syndrome caused by bronchial carcinoid that developed Cushing syndrome. METHODS: We performed several imaging studies, including chest and abdominal CT, for exploration of nodules and selective pulmonary arterial sampling for localizing a source of ectopic ACTH production. RESULTS: The patient was diagnosed as Cushing syndrome due to ectopic production of ACTH without identification of its source(s). After 2 years' follow-up with repeated CT scans every 6-12 months and treatment with metyrapone, chest CT revealed two small nodules respectively in the segment (S) 4 and 10 of the right lung. We performed selective pulmonary arterial sampling from branches of the right pulmonary artery to obtain blood from the nodules in a reverse flow fashion: wedged sampling from the basal branch (A8, 9 and 10) revealed significant elevation of ACTH, whereas sampling from the lateral branch (A4) did not, indicating that the S10 nodule produced ACTH ectopically. The video-assisted thoracoscopic surgery removing the right inferior lobe normalized plasma ACTH, serum cortisol and 24-hour urinary free cortisol. The S10 nodule was histologically diagnosed as atypical bronchial carcinoid containing immunoreactive ACTH. CONCLUSIONS: Selective pulmonary arterial sampling was useful for localizing the lesion of ectopic ACTH production and helped make the decision for its surgical removal. This procedure should be considered once lung nodules suspicious for ectopic ACTH production are identified in patients with EAS.

Key words: Bronchial carcinoid, Cushing syndrome, Ectopic ACTH syndrome, Pulmonary arterial sampling

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INTRODUCTION

Ectopic ACTH syndrome (EAS) causes cortisol over-production from the adrenal glands and develops Cushing syndrome (CS).[1] It underlies 10-20% of all CS cases.[2] Various kinds of nodules, ranging from undetectable benign lesions to widespread metas-

tases, are reported to develop EAS.[3] EAS is often associated with severe hypercortisolemia and thus develops a life-threatening form of CS.[4,5] Localizing the source of ectopic ACTH production is critical for treating biochemical and metabolic abnormalities caused by hypercortisolemia.[3] We previously reported that selective venous sampling was essential for localizing ectopic ACTH production to a malignant paraganglioma, which was identified with several imaging procedures, such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI).[6] Here we report another case with EAS caused by atypical bronchial carcinoid whose ectopic ACTH production was successfully identified with selective pulmonary arterial sampling. Finding sources of ectopic ACTH production with selective vascular catheterization is key for both accurate diagnosis of EAS and subsequent surgical resection of ACTH-producing lesions.

CASE PRESENTATION

A 42-year old man was admitted to the Yokohama Rosai Hospital for evaluation of his hypertension and pathological fractures that started about 3 years ago. On examination, he demonstrated hypertension (160/98 mmHg), moon face, abdominal red striae and peripheral edema. His body mass index was 28.2 kg/m^2. He also had diabetes mellitus, which was confirmed with 75g OGTT. He showed elevated white blood cell counts (10200/μl) with neutrophilia (89%), hypokalemia (3.2 mEq/l), dyslipidemia and metabolic alkalosis. Bone X-ray and DEXA revealed thoracic vertebral fractures and osteopenia (T-score -1.68).

In endocrinological examination, his plasma ACTH (123 pg/ml, normal 7.2~63.3) and serum cortisol (34.7 μg/dl, normal 4~18.3) concentrations were elevated without diurnal fluctuations, whereas these hormones did not respond to overnight suppression with low- or high-dose (1 and 8 mg, respectively) dexamethasone or intravenous injection of the ovine corticotropin-releasing hormone (CRH) (100 μg). Twenty-four-hour excretion of urinary free cortisol was 537 μg/day (normal 11.2~80.3). No mass lesions were detected in pituitary MRI. CRH injection-assisted bilateral inferior petrosal sinus sampling did not identify abnormal ACTH elevation. The patient was thus diagnosed as EAS based on these laboratory findings.

To explore the lesion(s) of ectopic ACTH production in our case, various imaging studies were performed. Chest and abdominal CT scans revealed no abnormal masses. FDG-PET and thallium perfusion scintigraphy did not identify any abnormal uptakes either. No significant lesions were also found with gastro-intestinal endoscopy and colonoscopy. Further, whole body venous catheterization failed to detect abnormal ACTH secretion. Tumor markers, such as the carcinoembryonic antigen, neuron-specific enolase, pro-gastrin-releasing peptide and the 5-hydroxyindoleacetic acid, were all within normal ranges.

Since we could not identify the source of ectopic ACTH production at the time of presentation, we treated the patient with metyrapone (4 g/day), an inhibitor of 11β-hydroxylase for suppressing adrenal cortisol production, and followed him up with regular examinations (every 6-12 months) with chest and abdominal CT scans. Two years after initial evaluation, chest CT revealed a small nodule in the S4 segment of the right lung (Figure 1a). We performed selective pulmonary arterial sampling, but no abnormal elevation of ACTH levels were identified at that time. Later, careful examination of the CT image by

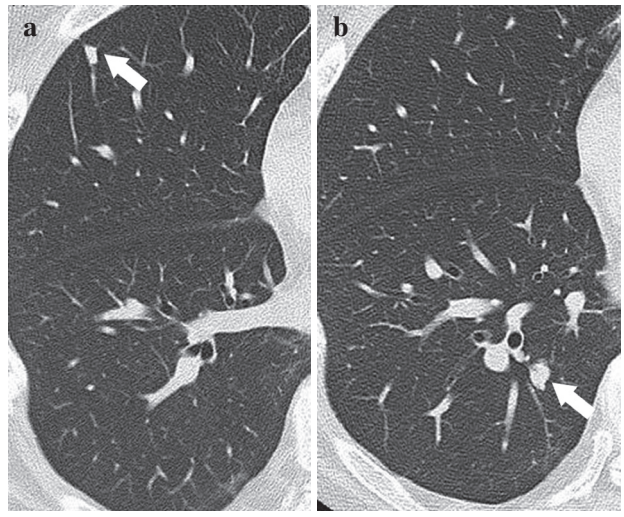

Figure 1. (**a**) A chest CT image obtained two years after initial evaluation. Arrow indicates a small nodule found in the S4 segment of the right lung. (**b**) The different slice of the same CT study as Figure 1 (a) that includes the S10 nodule. Arrow indicates the S10 nodule found in the right lung.

a well-trained radiologist identified a much smaller nodule in the S10 segment of the right lung (Figure 1b). We repeated the selective pulmonary arterial sampling. At this time, a blood sample was selectively withdrawn from the wedged right basal branch (A8, 9, 10), which was thought to feed the S10 nodule. Marked elevation of plasma ACTH concentrations was found in this blood (4200 pg/ml) in contrast to the samples obtained from the superior vena cava, inferior vena cava and the right lateral basal branch (A9) (260, 281 and 183 pg/ml, respectively) (Figure 2). These results suggested that the S10, but not S4, nodule secreted ACTH ectopically. Therefore, we performed video-assisted thoracoscopic surgery and resected the right lower lobe. The S10 nodule was 13 mm in its largest diameter and was histologically diagnosed as an atypical carcinoid with mitosis without necrosis (Figure 3). In immuno-histochemical analysis, this tumor was positive for ACTH, chromogranin A, synaptophysin, and CD56. The MIB-1 labeling index was 5%. The endocrinological examination performed one week after the operation revealed that the levels of plasma ACTH (1.9 pg/ml), serum cortisol (4.9 μg/dl) and 24-hour urinary free cortisol (9.8 μg/day) all fell dramatically. We subsequently started glucocorticoid replacement therapy. His clinical manifestations including moon face, hypertension and diabetes mellitus completely disappeared or were dramatically improved during follow-up.

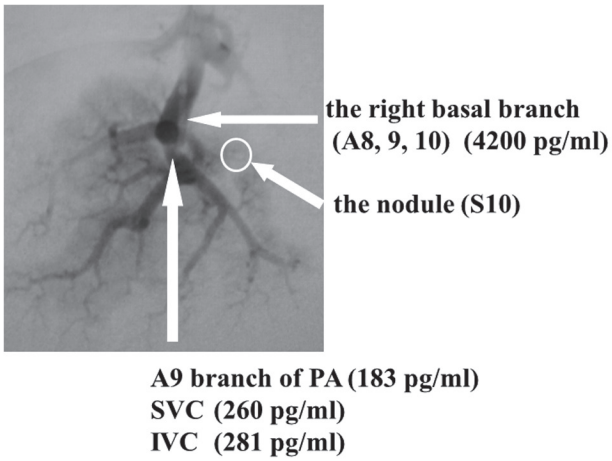

Figure 2. Selective pulmonary arterial sampling. Plasma ACTH levels in blood samples obtained from the right basal branch (A8, 9, 10), right lateral basal branch (A9), superior vena cava (SVC) and inferior vena cava (IVC) are shown. Plasma ACTH concentrations are shown in parentheses.

DISCUSSION

Various neoplasms originated in a variety of organs and tissues develop EAS.[3] Many of them are of neuroendocrine precursor cell origin, and bronchial carcinoids are the most common tumors among them (>25%). These carcinoids are usually small and are therefore difficult to detect with regular imaging procedures.[7] Thus, tumors with ectopic ACTH production sometimes remain unidentified despite intensive exploration and after long follow-up in a significant number (12.5%) of patients.[3] In agreement with this statistical information, various diagnostic procedures, such as CT, MRI, endoscopic intestinal examination,

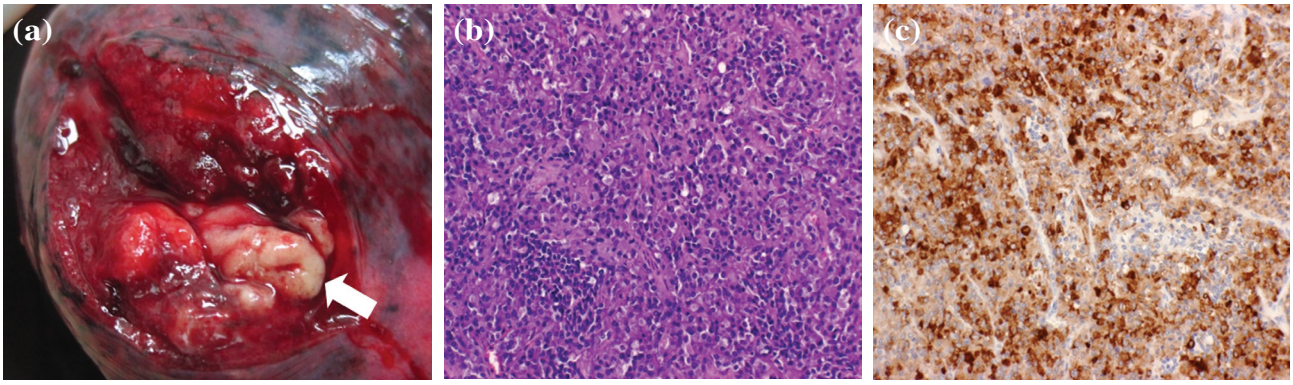

Figure 3. **(a)** Gross view of the patient's bronchial carcinoid in the resected lung. **(b)** Microscopic view of the patient's bronchial carcinoid in hematoxilin & eosin staining. **(c)** Detection of immunoreactive ACTH in patient's bronchial carcinoid in immunohistochemical staining. The same tissue section as (b) is used. Brown staining indicates ACTH.

thallium perfusion scintigraphy, FDG-PET and even whole body catheterization-assisted venous sampling, initially failed to identify ACTH-producing tumors in our case. We followed up the patient by treating with metyrapone and by repeating imaging studies every 6-12 months. Treatment with inhibitors of steroidogenesis may be helpful for identifying ACTH-producing tumors as they reduce production of adrenal cortisol, which in turn facilitates ACTH production and, possibly, growth of tumors, although these are adverse effects.[4]

Once lesions suspicious for ectopic ACTH production are found with various imaging procedures, the next step is to confirm ectopic production of ACTH from the identified nodules. Imaging procedures including CT and MRI scans are unable to distinguish ACTH-producing tumors from those without production.[8] Octreoscan has been employed as a useful tool for identifying the lesion of ectopic ACTH production, even in those patients who do not demonstrate nodules in regular imaging studies.[9] Octeroscan is especially useful for identifying neuroendocrine tumors like bronchial carcinoids, as these tumors preferentially express somatostatin receptor subtype (SSTR) 2 or 5, which bind radiolabeled octreotide similarly to their true ligand somatostatin (positive predictive values: 79%).[8,10] Among lung neuroendocrine tumors, SSTR 2 and 5 decrease expression from low-grade/intermediate-grade to high-grade tumors.[11,12] About 20% of bronchial carcinoids do not express SSTR 2 and 5,[13] whereas overall sensitivity of octreoscan for detecting ectopic ACTH-producing tumors is 57%.[8] We did not perform octreoscan in our case as the patient's ACTH did not respond to octreotide. FDG-PET remains complementary for identifying occult tumors because these nodules are sometimes metabolically active and uptake FDG efficiently (sensitivity 64%, positive predictive values 53%).[8] Whole body catheterization is technically difficult and of limited importance if the nodules are not identified.[3]

Selective pulmonary arterial sampling was very helpful to determine the ACTH-producing nodule in our case. Selective pulmonary arterial sampling was also reported to be useful for diagnosing ACTH-producing lesions in two cases with EAS (Table 1).[14,15] With this procedure, we can collect reverse flow blood from the tumors by wedging branches of the pulmonary artery and evaluate ectopic ACTH production of the tumors.[14,15] Thus, selective pulmonary arterial sampling should be considered as one of the most valuable diagnostic procedures for localizing ectopic ACTH production. In addition to this procedure, transbronchial or CT-guided transthoratic biopsy as well as the biopsy in combination with thoracoscopy may be helpful in some cases for immunohistochemical detection of ectopic ACTH in identified tumors.[16]

CONCLUSIONS

Initial failure to identify ACTH-producing nodules is common in patients with EAS.[7] The failure may suggest presence of bronchial carcinoids as causative tumors because they are the most prevalent neoplasms causing EAS, while they are also usually small and are thus difficult to find with regular imaging procedures.[4] The failure may however indicate

Table 1. Clinical profiles of two previously reported subjects and a current case whose ectopic ACTH production was successfully localized with the pulmonary arterial sampling (PAS).

			Characteristics of tumors			Plasma ACTH concentrations at the indicated vasculatures accessed with PAS	
Year	Reference	Age/sex	Pathology	Location in the lung	Size (diameter)		
2003	Sakurada et al[14]	47/F	Carcinoid	Rt. S3b	8 mm	A3 622 pg/ml	IVC 293 pg/ml
2010	Sugiyama et al[15]	69/F	Carcinoid	Rt. S5	7 mm	A5 4760 pg/ml	IVC 121 pg/ml
2013	Current case	44/M	Carcinoid	Rt. S10	13 mm	Inferior branch 4200 pg/ml	IVC 281 pg/ml

IVC: inferior vena cava

better prognosis of the patients as most of branchial carcinoids are benign and surgically removable due to their small size.[4] Imaging studies, such as CT scan (slice thickness: 2mm) every 6-12 months, should be performed till tumors are identified together with adequate treatment for hypercortisolemia using chemical compounds like metyrapone. Once tumors are identified, their ACTH production should be evaluated prior to surgical intervention. We report in this manuscript that selective pulmonary arterial sampling was useful for finding ectopic ACTH production from the patient's bronchial carcinoid. This procedure should be considered in any case with EAS whose lung tumors suspicious for ectopic ACTH production are identified.[16]

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DECLARATION OF INTEREST

The authors have nothing to declare as to conflict of interest.

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