Gavin Publishers
Gavin Journal of Oncology Research and Therapy
Volume 2016; Pages 4
Fierro-Maya F et al.

Case Report

Ectopic Cushing Syndrome Treated with Radio-Guided Occult Lesion Localization (ROLL) and Robotic Assisted Surgical Resection

Felipe Fierro-Maya[1]*, Garavito-González Gloria[1], Rojas-Melo Leonardo[1], Sandra Mora-Thiriez[2], Ricardo Buitrago[3], Alejandro Marti-Samper[4] and Alfredo Romero-Rojas[5]

[1]Department of Endocrine Oncology, Instituto Nacional de Cancerologia, Bogota, Colombia

[2]Endocrinologist, Universidad Nacional de Colombia, Bogota, Colombia

[3]Department of Thoracic Surgery, Instituto Nacional de Cancerologia, Bogota, Colombia

[4]Department of Nuclear Medicine, Instituto Nacional de Cancerologia, Bogota, Colombia

[5]Department of Pathology, Instituto Nacional de Cancerologia, Bogota, Colombia

***Corresponding author:** Felipe Fierro-Maya, Department of Endocrine Oncology, Instituto Nacional de Cancerologia, Cl. 1a #9-85, Bogotá, Colombia, Tel: +5714320160 E-mail: ffierro@cancer.gov.co

Citation: Fierro-Maya F, Gloria GG, Leonardo RM, Mora-Thiriez S, Buitrago R, et al. (2016) Ectopic Cushing Syndrome Treated with Radio-Guided Occult Lesion Localization (ROLL) and Robotic Assisted Surgical Resection. Gavin J Oncol Res Ther 2016: 10-13.

Received: 18 May, 2016; **Accepted:** 02 June, 2016; **Published:** 16 June, 2016

Abstract

We describe a patient with an Ectopic Cushing's Syndrome caused by a bronchial typical carcinoid. Radio-Guided Occult Lesion Localization (ROLL) with 99-Technetium technique was used during the thoracoscopic exploration and resection of the tumor with assistance of the surgical Davinci robotic system. After surgery, cortisol and other metabolic disturbances normalized.

Context: To show the benefit in the use of ROLL technique with the Robotic resection and bronchoplasty in the neuroendocrine tumor producing Ectopic ACTH Syndrome (EAS).

Keywords

Ectopic Cushing's Syndrome; Neuroendocrine tumor; Paraneoplastic syndrome; Radio Guided Occult Lesion Localization (ROLL technique), Robotical surgical procedures

Case Report

A 41 year-old man presented with a six-year history of weight gain, approximately 20 kg, moon-facies, purple striae, and proximal muscle weakness. His blood pressure was 154/92 mmHg, weight was 108 kg, body mass index 37 kg/m^2.

Biochemical evaluation revealed: normal electrolytes, high blood glucose (160 mg/dl), normal liver enzymes; 24h urinary cortisol was 1089 µg/24hrs (normal: 4-176 µg/24hrs). 8:00 am cortisol was 21.4 µg/dl after 1 mg dexamethasone suppression test (considered abnormal when >1.8 µg/dl). ACTH was 68 pg/ml (normal values: 5-65). A High-Dose 2 day Dexamethasone Suppression Test (HDDST) was done and showed a not suppressed serum cortisol (10.2 µg/dL) and the reduction was less than 50% with respect of the basal cortisol (18.7 µg/dl,

ACTH	RPS	LPS	RPS/LPS	Peripheral	PS/Peripheral
Basal	19.8	2.76	6.8	14	1.4
2 min	117.9	95	1.23	43.7	2.7
3 min	57.5	80	0.64	80	0.7
10 min	63.4	73.7	0.85	192	0.3

Table 1: Bilateral Inferior Petrosal Sinus Sampling (BIPSS) with desmopressin 10µg iv bolus. The patient had a Basal ACTH IPS: P ratio less than 2, and Maximal post-stimulation IPS: P ratio less than 3 (No central gradient).

RSP: Right Petrosal Sinus; LSP: Left Sinus; RPS/LPS: Right/Left Petrosal Sinus Relation; PS: Petrosal Sinus

normal values: 5-25µg/dl). Pituitary Magnetic Resonance Imaging (MRI) revealed no abnormality. The inferior petrosal sinus catheterization results are shown in table 1.

A Chest Computed Tomography with contrast showed no lesions, but ^{99}Tc-Hydrazinonicotinyl-Tyr3-Octreotide HYNIC-TOC/SPECT-CT scintigraphy found a focal lesion in the posterior segment of left lower lung lobe (Figure 1).

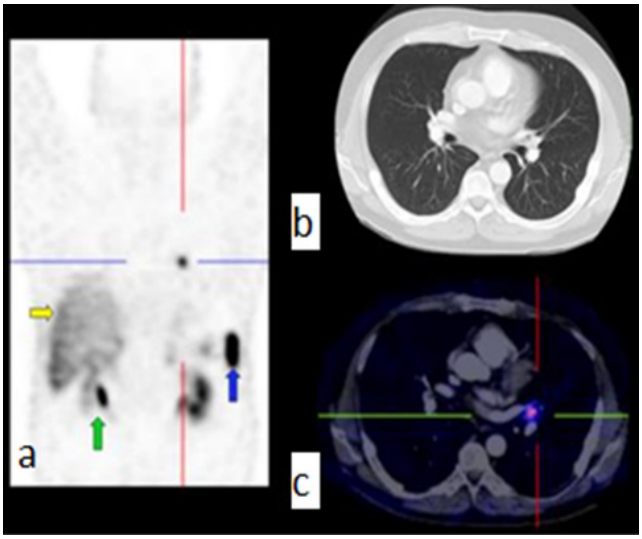

Figure1: 99mTc-HYNIC-TOC somatostatin receptor scintigraphy.

a) Coronal slice that shows a focal uptake in the left lung (red and light blue cross triangulation), physiologic uptake in liver (yellow arrow), kidney (green arrow) and spleen (blue arrow).

b) Axial slice showing a round mass located within the lower lingular bronchus in the CT.

c) Fusion image of CT and scintigraphy demonstrating high radiopharmaceutical uptake in the lesion because of over expression of somatostatin receptors.

The patient underwent a Radio-guided Occult Lesion Localization (ROLL) with ^{99}Technetium labeled macroaggregated albumin (MAA-Tc99m) 0.2ml: 300µCi intratumoral with assistance of the surgical Davinci robotic system, followed by a flush of 0.2 ml of saline solution. Because of the high particle size of this MAA-Tc99m which ranges between 10 to 150μm it is assured that the radio pharmaceutical will remain trapped inside the tumor for adequate localization with negligible escape to the lymphatic system, which means less noise interference, using this technique the lesion is well centered and amenable for radioguided detection using the sentinella gamma probe.

A lesion on the wall of the lingula's bronchus was detected as the source of radioactivity. Resection was done using the multi-wrist instruments of the robot (Figure 2).

The wall defect in the bronchus was repaired by bronchoplastic procedure, preserving the lung parenchyma. Lung re-expansion was achieved. Admission to the Intensive Care Unit (ICU) was not required. The chest tube was removed 24 hours after surgery. Pathology report demonstrated a neuroendocrine tumor, with vascular invasion but no mitotic activity or necrosis. Two peribronchial lymph nodes showed no

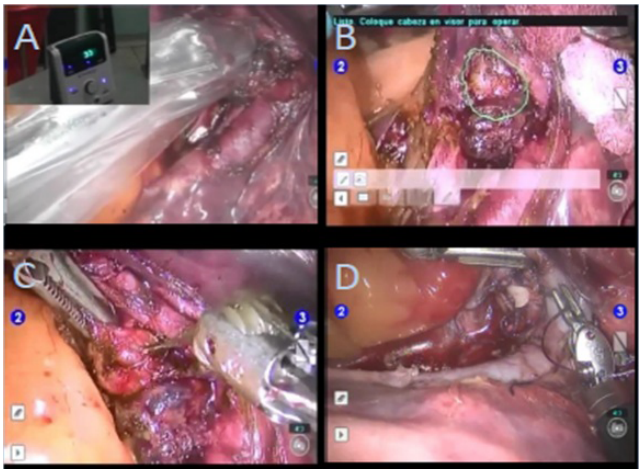

Figure 2: Tumor resection with ROLL with 99-Technetium labeled macroaggregated albumin intratumoral with assistance of the surgical Davinci robotic system.

A: Left thoracoscopy with DaVinci robotic assistance, localization of tumor with Gamma Probe (box);

B: Gray circle shows identification of the tumor after removal;

C: Resection of the tumor with robotic instruments;

D: Bronchial wall closure where the tumor was located (Bronchoplasty) preserving pulmonary lobules; adequate closure was verified.

metastases. The tumor stained positively for CAM 5.2, synaptophysin, Chromogranine A, CD5 and ACTH; the tumor immuhistochemistry was negative for CD117, TTF-1 and CDX2; Ki-67 was of 1% (Figure 3).

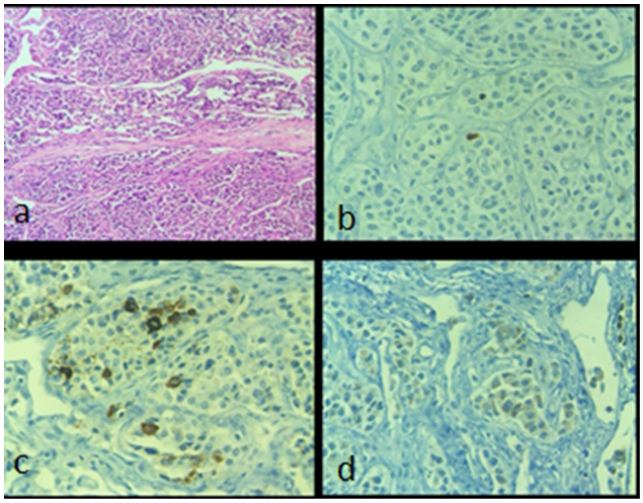

Figure 3: Pathological data of the case: a) Hematoxylin-Eosin Original magnificationX10, showing a morphologically well differentiated neoplasm with a nesting pattern; b) KI-67 immunostaining (hot spot) giving a Ki67 index of 1%; c) Immunostaining revealing strong positivity for ACTH in the tumor cells, and d) Immunostaining showing positivity for CD5 in the tumor cells.

These results supported a Typical Carcinoid tumor of thymic origin due to CD5 expression (Figure 3). The patient's clinical manifestations improved, the patient lost weight, his hypertension and diabetes mellitus were cured. After two years of follow up, the patient remains with no evidence of disease.

Discussion

This is at the present, the first published case of a bronchial carcinoid tumor localized with the ROLL technique and treated robotically. The reason to use these techniques was the no visualization of any lesion on CT but visible by HYNIC TOC scintigraphy, favoring the option to preoperatively mark the lesion with ^{99}Tc to perform then, a minimally invasive procedure.

Cushing Syndrome (CS) is a disease characterized by abnormally elevated cortisol concentrations in plasma. This disorder is associated with a five-fold increase in cardiovascular mortality due to atherosclerosis, hypertension, insulin resistance, diabetes mellitus type 2 and dyslipidemia, increased risk of infections, osteoporosis, thromboembolic phenomena, and psychiatric disorders [1]. ACTH dependent CS can be originated from pituitary adenoma (Cushing's disease) or from an ectopic source of ACTH (EAS).

The EAS is an unusual and severe type of CS [2,3]. The major proportion of patients with EAS (48.9%) is caused for small cell cancers of the lung and bronquial carcinoids [4]. Less common causes include thymic carcinoids, which represent 7% in the different series [5,6]. An occult tumor causing EAS has been reported in up to 10% of the cases [4].

In not severe cases, as in our patient, there are major challenges in the diagnostic approach and no single biochemical test is accurate by itself to discriminate between CD and EAS [6,7]. Although ACTH levels from ECS are usually higher than those from CD, there is no approved cutoff point to differentiate them [8]. Hypokalemia is another feature of EAS but is not present in up to 30% of the patients [4,7]. The HDDST is widely used to differentiate these entities [9], but it might be inaccurate in 6-14% of cases, particularly in patients with pulmonary carcinoids [7]. CRH testing seems to be more specific, with false positive results only in 8-9% [7,10]. Bilateral Inferior Petrosal Sinus Sampling (BIPSS) is the best tool for the differentiation between CD and ECS etiologies, although anomalous venous drainage might yield false negative results [7,11]. Usually a central: peripheral ACTH gradient is considered ≥ 2 at basal levels and ≥ 3 after desmopressin stimulation, indicating a central origin, and lateralization is defined as an intersinus gradient ≥1,4 [12]. In a meta-analysis that involved 21 studies, the overall sensitivity was 96% and the specificity was 100% [3]. In other studies, the false negative rate to find a central: peripheral gradient has been reported between 3% to 8% of patients with Cushing's disease [4,12].

Obtaining images is the second step after the diagnosis EAS is confirmed, with cross sectional imaging such as Computed Tomography (CT) or Magnetic nuclear Resonance Imaging (MRI) of neck, thorax and abdomen being recommended, with a sensitivities of 93% (79-98%) and 90% (74-96%) respectively [13]. When the mentioned images fail in detect the lesion, a scintigraphy with radiolabeled somatostatin analogs (SST2 scintigraphy) can localize ACTH producing neuroendocrine tumors with sensitivity between 49 to 60% specially in those with low histologic grade 1 or 2 (WHO 2010) [7,14-16]. The low sensitivity of SST2 scintigraphy is explained by the down regulation of SST2 receptors because of hypercortisolism, which is reversible after eucortisolemia restoration.

With the use of 68-Galium DOTATAE PET-CT, the sensitivity could increase to 96% [16]. Sometimes a [(18)F] FluoroDeoxyGlucose (FDG)-Positron Emission Tomography (PET) has been used in the attempt to localize the lesion in NET with a sensitivity of64% (35 -85%) [13].

After localization, curative surgery must be attempted. According to the different series this is feasible in 71% cases, with one-third of the patients achieving complete remission one month afterward [17]. In the case presented here in, we find a small peribronquial tumor classified as a Typical Carcinoid of thymic origin due to CD5 expression by immunohistochemistry [18].

With the use of localization and labeling of the abnormal tissue using nuclear medicine and robotic aid with three-dimensional vision and multiarticulated instruments was possible to dissect, remove tumor and perform he reconstruction of the structures through a minimal invasive surgery, and more efficiently than an open or conventional video assisted thoracic surgery.

This technological aid permitted no admission to Intensive care unit and only two days of hospital stay. There is a previous report by Schmid T and cols of a hybrid video-assisted thoracic surgery-robotic minimally invasive right upper lobe sleeve lobectomy [19]. This is at the present the first published case of a low grade neuroendocrine tumor locallized with ROLL technique and treated robotically.

References

1. Lindholm J, Juul S, Jørgensen JO, Astrup J, Bjerre P, et al. (2001) Incidence and late prognosis of Cushing's syndrome: apopulation-based study. J Clin Endocrinol Metab 86: 117-123.
2. Wajchenberg BL, Mendonca B, Liberman B, Adelaide M, Pereira A, et al. (1995) Ectopic ACTH syndrome. J Steroid Biochem Mol Biol 53: 139-151.
3. Newell-Price J, Trainer P, Besser M, Grossman A (1998) The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev 19: 647-672.
4. Ejaz S, Vassilopoulou-Sellin R, Busaidy NL, Hu MI, Waguespack SG, et al. (2011) Cushing's syndrome secondary to ectopic ACTH secretion: The University of Texas MD Anderson Cancer Center Experience. Cancer 117: 4381-4389.
5. Aniszewski JP, Young WF, Thompson GB, Grant CS, van Heerden JA (2001) Cushing's syndrome due to ectopic adrenocorticotropic hormone secretion. World J Surg 25: 934-940.
6. Isidori AM, Kaltsas GA, Pozza C, Frajese V, Newell-Price J, et al. (2006) The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. J Clin Endocrinol Metab 91: 371-377.
7. Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, et al. (2005) Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab 90: 4955-4962.

8. Pivonello R, De Martino MC, De Leo M, Lombardi G, Colao A (2008) Cushing's syndrome. Endocrinol Metab Clin North Am 37: 135-149.

9. Aron DC, Raff H, Findling JW (1997) Effectiveness versus efficacy: the limited value in clinical practice of high dose dexamethasone suppression testing in the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab 82: 1780-1785.

10. More J, Young J, Reznik Y, Raverot G, Borson-Chazot F, et al. (2011) Ectopic ACTH Syndrome in Children and Adolescents. J Clin Endocrinol Metab 96: 1213-1222.

11. Oldfield EH, Doppman JL, Nieman LK, Chrousos GP, Miller DL, et al. (1991) Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. N Engl J Med 325: 897-905.

12. Machado MC, de Sa SV, Domenice S, Fragoso MC, Puglia P, et al. (2007) The role of desmopressin in bilateral and simultaneous inferior petrosal sinus sampling for differential diagnosis of ACTH-dependent Cushing's syndrome. Clin Endocrinol (Oxf) 66: 136-142.

13. Zemskova MS, Gundabolu B, Sinaii N, Chen CC, Carrasquillo JA, et al. (2010) Utility of various functional and anatomic imaging modalities for detection of ectopic adrenocorticotropin secreting tumors. J Clin Endocrinol Metab 95: 1207-1219.

14. Torpy DJ, Chen CC, Mullen N, Doppman JL, Carrasquillo JA, et al. (1999) Lack of utility of 111-In-pentetreotide scintigraphy in localizingectopic ACTH producing tumors: follow-up of 18 patients. J Clin Endocrinol Metab 84: 1186-1192.

15. Tsagarakis S, Christoforaki M, Giannopoulou H, Rondogianni F, Housianakou I, et al. (2003) A Reappraisal of the Utility of Somatostatin Receptor Scintigraphy in Patients with Ectopic Adrenocorticotropin Cushing's Syndrome. J Clin Endocrinol Metab 88: 4754-4758.

16. Etchebehere EC, de Oliveira Santos A, Gumz B, Vicente A, Hoff PG, et al. (2014) 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-Octreotide SPECT/CT, and Whole-Body MR Imaging in Detection of Neuroendocrine Tumors: A Prospective Trial. J Nucl Med 55: 1598-1604.

17. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, et al. (2008) Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement. J Clin Endocrinol Metab 93: 2454-2462.

18. Hishima T, Fukayama M, Fujisawa M, Hayashi Y, Arai K, et al. (1994) CD5 expression in thymic carcinoma. Am J Pathol 145: 268-275.

19. Schmid T, Augustin F, Kainz G, Pratschke J, Bodner J (2011) Hybrid video-assisted thoracic surgery-robotic minimally invasive right upper lobe sleeve lobectomy. Ann Thorac Surg 91: 1961-1965.