Ectopic ACTH syndrome in lung carcinoids – a case series

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Introduction

Ectopic ACTH secretion accounts for 10-20% of endogenous Cushing's syndrome (CS). More often its source is located to the lung, associated with highly malignant tumors or with less aggressive variants of neuroendocrine tumors, carcinoid tumors. Here we present a case series of 6 patients with ectopic Cushing's syndrome due to lung neuroendocrine tumors.

Case description

All cases of ACTH-producing lung carcinoid/tumorlets diagnosed in the past 20 years at Hospital São João, Porto, Portugal were analyzed. Figure 1 and Table 1 summarizes the main physical and laboratory findings at diagnosis of all patients. All but one had cushingoid features. ACTH-dependent hypercortisolism was confirmed in all patients. Magnetic resonance imaging (MRI) was performed in all but 1 cases (case 6) and showed normal pituitary gland.

Case 1

A 41 year-old male presented a 2 years history of loss of libido. Bilateral inferior petrosal sinus sampling (BIPSS) suggested ectopic origin of ACTH. Evaluation with 68Ga-DOTA-TOC PET/CT showed a nodule in the superior lobe of the left lung (SLLL). He underwent lobectomy and remains free from disease 32 months following surgery. Last year he has been diagnosed with thymic hyperplasia upon an incidental finding on a routine follow-up scan. He's doing well except for complains of general fatigue.

Case 2

A 47 year-old female presented a 12 months history of menstrual irregularities, weight gain and psychiatric changes (depression, psychosis). BIPSS suggested ectopic origin of ACTH. A CT-scan showed a 12 mm nodule in the SLLL. She underwent lobectomy and remains well and free from disease 14 years following diagnosis.

Case 3

A 44-year-old female was admitted with septic shock from pulmonary origin. She complained of a 4 months history of fatigue, headaches, weight gain and hirsutism. BIPSS suggested ectopic origin of ACTH. Evaluation with 68Ga-PET and PET-FDG failed to identify the source. As she presented uncontrolled hypercortisolism despite treatment with steroidogenesis inhibitors, she underwent bilateral adrenalectomy 6 months following CS diagnosis. Five years later, a CT scan showed a lung lesion (not hypercaptating in 68Ga-DOTA PET). The mass was biopsied and pathology showed an ACTH expressing carcinoid tumor.

Case 4

A 37 year-old male complained with weight gain, headaches, fatigue and leg edema for 5 months. A CT-scan identified a 30 mm lesion at the SLLL. Pathological study of the lesion was compatible with lung carcinoid. Despite initial improvement, 9 months following surgery there was clinical and biochemical evidence of disease recurrence. Ga-PET showed new hypercaptating lesions at multiple locations (bone, lymph nodes). The disease stills shows signs of progression despite treatment with lanreotide and everolimus. He is currently awaiting adrenalectomy for symptomatic control

Case 5

A 75 year-old female was referred to our department for the study of an adrenal incidentaloma. Biochemical workup showed elevated ACTH levels suggesting ACTH dependent CS and a HDDST was suggestive of an ectopic origin. A somatostatin receptor scintigraphy identified a lesion in the left lung. Eleven years after surgery she remains free of disease. She is now 88 years-old.

Case 6

A 73-year old women with a history of DIPNEHC, was admitted for severe hypokalemia and peripheral edema that started the previous month. Clinical suspicious of CS was raised and an ectopic origin for ACTH was suggested by HDDST. 68Ga-PET identified multiple hypercaptating lesions. Pathology of one of the lung lesions revealed a carcinoid tumour and the hepatic biopsy identified a lesion compatible with metastasis. Despite a initially promising response to lanreotide, 12 months following diagnosis she died of septic shock following an orthopedic intervention.

Table 1 Summary of Characteristics and Laboratory Findings at Presentation

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Normal range
Age at diagnosis	41	47	44	37	75	73	
Sex	Male	Female	Female	Male	Female	Female	
de novo Hypertension	Yes	Yes	No	Yes	No	Yes	
de novo Hyperglycemia HA1c %	No N.A.	Yes 6.2	Yes 7.5	Yes 5.8	Yes 7.8	Yes 8.8	 <6.5
Serum potassium (mEq/L)	3.9	3.1	2.2	3.0	2.9	2.2	3.5-5.1
Serum cortisol (ug/dL) 0 am 8 am 4 pm	 25.2 28 27.3	 N.A. 61.5 67.2	 125 158.2 N.A.	 N.A. 34.6 N.A.	 N.A. 42 27.8	 83.4 112.6 110.2	 1.7-8.9 6.2-19.4
Serum ACTH (ng/L) 0 am 8 am 4 pm	 N.A. 112 99.8	 N.A. 239 204	 N.A. 698 N.A	 N.A. 105 N.A	 N.A. 105,7 165.2	 N.A. 167.5 239.8	 <63.3
Urinary free cortisol (ug/day)	610.8	1395	>5038	836	2008	3648	36-137
LDDST serum cortisol serum ACTH urine free cortisol	 18.6 107.6 311.3	 28 136 575	 N.A. N.A. N.A.	 N.A. N.A. N.A.	 17.7 39.6 N.A	 77.5 N.A. N.A.	 <1.8
HDDST serum cortisol serum ACTH urine free cortisol	 14.6 (58.4%) 115.1 90.6 (15%)	 N.A. N.A. N.A.	 N.A. N.A. N.A.	 N.A. N.A. N.A.	 47.2 (112%) 80.5 1474 (73%)	 61.4 (73.6%) 211.4 11988 (328.6%)	 <50% <50%
BIPSS central/peripheral ACTH basal central/peripheral ACTH after stimulation	 1.2 1.48	 1.1 1	 1.6 1.7	 N.A. N.A.	 N.A.	 N.A.	 > 2 > 3

|LDDST: low dose dexamethasone suppression test |HDDST: high dose dexamethasone suppression test | BIPSS: bilateral inferior petrosal sinus sampling

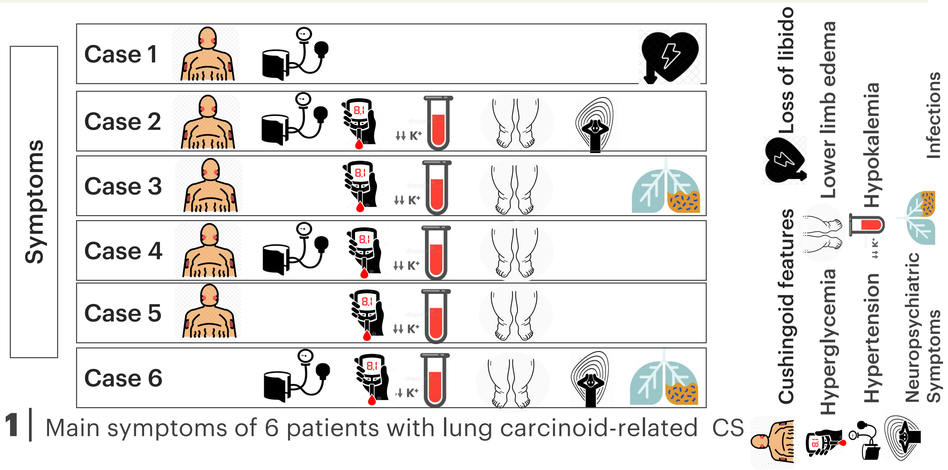

Figure 1 | Main symptoms of 6 patients with lung carcinoid-related CS

Table 2 | Patient and Tumour Characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Symptom's onset to diagnosis (months)						
- CH	24	12	6	3	36	3
- Lung carcinoid	29	19	60	7	48	6
Tumor diameter (cm)	0.9	1.2	1.7	3.3	2.5	0.8*
Tumor subtype	TC	AT	TC	TC	TC	Unknown**
Metastases	None	None	None	None	None	Liver, bone
Stage at surgery	IA	IA	IA***	IB	IA	IV
Surgery type	lobectomy	lobectomy	lobectomy	lobectomy	lobectomy	-
Follow-up (months)	32	180	84	60	132	--
Disease status	NED	NED	NED	DP	NED	DOD

|CH: Cushing's syndrome |TP: typical carcinoid |AT; atypical carcinoid |NED: No evidence of disease |DP: Disease progression |DOD: Died of disease |
* The patients had multiple lung lesions. The largest is represented.
** Definitive diagnosis was not possible because the patient did not undergo surgery.
*** For this patient the source of ACTH has remained occult for 5 years. She initially underwent bilateral adrenalectomy for symptomatic control.

Table 3 | Imaging study performed for each patient at diagnosis-

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Thorax CT scan	9 mm lesion SLLL	12 mm lesion SLLL	17 mm lesion ILLL	33 mm lesion SLLL	25 mm lesion ILLL	Multiple lesions (DIPNECH)
Somatostatin receptor scintigraphy (Octrotide^{111}In)	Equivocal results	No hypercaptating lesion	-	-	Hypercaptating lesion in ILLL	-
68 Ga-DOTA-TOC	9 mm lesion with discrete hypercaptation	-	Lesion at ILLL with no hypercaptation	-	-	Lesion SLLL + ILRL+ Liver + lymph nodes and bone lesions
18F-FDG-PET	No hypercaptating lesion	No hypercaptating lesion	No hypercaptating lesion	-	-	No hypercaptating lesion

| SLLL: superior lobe left lung | ILLL: inferior lobe of left lung | ILRR: inferior lobe of right lung

Concluding remarks

In our case series, the lag time between symptoms onset and CS diagnosis was highly variable (ranging from 3 to 24 months). Once ectopic-CS was established, tumor localization was generally prompter, except for the case where tumor origin was deemed occult at diagnosis. In this case (case 3), bilateral adrenalectomy allowed efficient symptomatic control enabling tumor localization and surgical management 5 years after diagnosis. In our case series, and in accordance with bibliography[1], lung carcinoids have excellent prognosis when surgery is an option. Four out of five patients with no evidence of metastasis at diagnosis and treated with surgery remain free of disease (median follow up 84 months). One of the patients (case 4) had disease progression with evidence of metastasis 9 months following surgery. This patient had the biggest tumor size at diagnosis (33 mm). Despite being the most common source of ectopic CS, lung carcinoid related ectopic CS remains a rare diagnosis. This case series aims to raise awareness for this entity.

Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol. 2015;26(8):1604-20.