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SIMULTANEOUSLY PRESENTATION OF TWO PARANEOPLASTIC SYNDROMES IN A PATIENT WITH LUNG CARCINOMA

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Abstract:

Introduction*: Paraneoplastic syndromes are frequently found in lung cancer and they can be the first manifestation of disease. We present the case of a patient with small cell lung cancer and two simultaneously paraneoplastic syndromes.*

Clinical case*: A 63 year old male patient presented with anorexia, confusion and vomiting. Laboratory investigations exhibited severe hyponatremia with high urinary sodium excretion in 24 h urine, normal serum creatinine and hepatic function, low uric acid, normal acid-base and potassium balance, normal thyroid and adrenal insufficiency excluded. In this context, the diagnosis of inappropriate anti-diuretic hormone secretion was confirmed. Computed tomography scan of the chest showed a left hilar mass and abdominal scan a large adrenal tumor. Histological and immunohistochemical aspects of the sample of transbronchial fine needle aspiration support the diagnosis of small-cell lung carcinomas. Hypercortisolism and lack of suppression on dexamethasone suppression tests in the context of high normal value of adrenocorticotropic hormone made a presumptive diagnosis that lung tumor was also secreting ectopic adrenocorticotropic hormone.*

Conclusion*: Patients that presented simultaneously with two or more paraneoplastic syndromes were rare. Our patient presented with hyponatremia induced by inappropriate secretion of anti-diuretic hormone as the first sign of a lung cancer, then further investigations revealed adrenal tumor and hypercortisolemia due to ectopic adrenocorticotropic hormone.*

Key words*: paraneoplastic syndrome, small-cell lung carcinomas, inappropriate secretion of antidiuretic hormone, ectopic adrenocorticotropic hormone.*

1. Introduction

The paraneoplastic endocrine syndromes ("ectopic" or "inappropriate" hormone production) comprise a wide range of symptoms associated with malignancy or less commonly benign tumors. Production of peptides by neuroendocrine tumors is

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the most common cause of the ectopic hormone syndromes. Neuroendocrine cells are spread in almost all organs of the body. More prevalent are lung, gastrointestinal tract, pancreas, thyroid gland, adrenal medulla, breast, prostate, and skin tumors [10]. Neuroendocrine cells are derived from neural crest and produce biogenic amines and polypeptide hormones. The hormones produced by these tumors derived from neuroendocrine cells includes ACTH, calcitonin, vasoactive intestinal peptide (VIP), bombesin, growth hormone-releasing hormone (GHRH), pancreatic polypeptide, corticotropin-releasing hormone (CRH), neurotensin, somatostatin (SRIH), antidiuretic hormone (ADH) and other small peptides [8, 10]. In a significant number of cases, small-cell lung carcinomas (SCLC) may produce ectopic hormones, including adrenocorticotropic hormone (ACTH) and anti-diuretic hormone (ADH). There are only few reported cases in the literature with simultaneously ectopic secretion of ACTH and inappropriate secretion of ADH (SIADH) [3, 11, 13]. We report the case of a patient with lung carcinoma that associates two paraneoplastic syndromes including SIADH and adrenocorticotropic hormone (ACTH).

2. Clinical case

A 63 year old man presented to the Emergency Department complaining of anorexia, confusion and vomiting. At the time of admission on internal department, he appeared lethargic and mildly confused. Laboratory examination revealed severe hyponatremia (109 mmol/L). The patient was admitted to the hospital for specialist care and electrolyte replacement. During hospitalization, although he received isotonic and hypertonic saline solution, hyponatremia has not corrected and his clinical condition has deteriorated. Computed tomography scan showed a large adrenal tumor. Internal medicine physician decides on the transfer to the department of endocrinology. On admission to the department of endocrinology the patient presented with high blood pressure and severe hyponatremia. Tests were care out to investigate the serious hyponatremia. Patient was clinical euvolemic without edema or ascites, with high urinary sodium excretion >190 mmol in 24 h urine, normal serum creatinine and hepatic function, low uric acid, normal acid-base and K balance, normal thyroid function and with adrenal insufficiency excluded (table 1). In this context, the diagnosis was suspected and confirmed to be inappropriate ADH secretion. Further investigations were needed to establish a possible tumor causes.

Table 1

Usual investigations on presentation

Investigations	Patient values	Reference values
WBC (10^3/µL)	4.07	4-10000
RBC (10^6/µL)	4.53	4-5.5
HGB (g/dl)	13.9	12-16
HCT (%)	36.5	35-53
VEM (fl)	80.6	83-103
MCH (pg)	30.7	28-34
MCHC (g/dl)	38.1	32-36
PLT (10^3/µL)	270	150-450
Lymphoytes (10^3/µL)	0.58	1-3.7
Glycemia (mg/dl)	107	75-105
Creatinine (mg/dl)	0.67	0.5-1.2
Urea (mg/dl)	20.77	10-50
Na^+ (mmol/L)	109	136-145
K^+ (mmol/L)	3.8	3.5-5.1
Cl^- (mmol/L)	80	101-110
Uric acid	1.29	2.4-8.4

His medical history included a diagnosis of hypertension (treated with lysinoprilum 10 mg per day) and diabetes mellitus (in treatment with oral hypoglycemic medication metforminum 1000 mg per day) and testicular carcinoma in 1987 that was successfully treated with chemotherapy and radiotherapy. Clinical examination of the scrotum was normal and laboratory investigations (PSA, HCG) were also in normal limits and pelvic ultrasonography was without pathological changes.

Restriction of fluid intake (about 500 ml/day) was initiated in patient with normal salt intake and loop diuretics. The clinical course was favorable with recovery of consciousness and with slow sodium correction from 114 to 139 mmol/L in approximately two weeks. All the time serum potassium levels were in normal range (table 2).

Electrolytes dynamic tests Table 2

	22.04.2013	9.05.2013	10.05.2013	12.05.2013	13.05.2013	14.05.2013	15.05.2013	20.05.2013
Na^+ (mmol/L)	109	114	118	121	135	134	137	146
K^+ (mmol/L)	3.9	4.8	4.4	3.86	4.4	4.3	4.4	4.5
Cl^- (mmol/L)	80	80	80	83.4	84	96	96	104

Plasmatic cortisol dynamic tests Table 3

Normal ranges of plasmatic cortisol	23 PM cortisol	Overnight 1 mg Dexamethasone suppression test	8 mg dexamethasone suppression test
AM: 101.2-535.7 nmol/L PM: 79-477.8 nmol/L	1440 nmol/L	1331 nmol/L	1295 nmol/L

Abdominal CT investigation revealed an 8/8.5 cm heterogeneous mass on left adrenal gland, imprecisely delimited suggesting a malignant tumor in the context of SIADH. Further investigation revealed on computed tomographic scanning of the chest a 9.8 cm left hilar mass. This investigation could not differentiate between tumor mass and hilar adenopathy. We indicated then transbronchial fine needle aspiration. Histological and immunohistochemical aspects (CD 56, TTF1 and CK 7 positive) support the diagnosis of SCLC. Cerebral MRI did not reveal any structural abnormality in the hypothalamic-pituitary area.

In the context of adrenal tumor with high blood pressure and the potassium in the normal range, the normal values of metanephrines (0.47 mg/24 hour urinary) excluded pheochromocytoma.

When we performed 1 mg dexamethasone suppression test we noticed that cortisol level failed to suppress and hypercortisolism was suspected and then confirmed by high midnight cortisol level and 24 hour urinary cortisol test (tables 3 and 4). The patient's cortisol also failed to suppress on 8 mg dexamethasone. High normal value of ACTH excluded hypercortisolism induced by adrenal tumor. Than we made a presumptive diagnosis that his lung tumor was secreting ectopic ACTH even in the absence of hypokalemia.

Table 4

24-hour urinary free cortisol

Normal values of 24-hour urinary free cortisol	Patient values
11.8 - 485.6 nmol/24h	1909 nmol/24 h

We consider that the two paraneoplastic syndromes (ACTH and SIADH) derived from lung cancer with adrenal metastasis. Ectopic ACTH secretion caused melanodermia, diabetes mellitus, and high blood pressure without hypokalemia and severe hyponatremia was induced by SIADH.

The patient was discharged to home with indication of fluid restriction (500-700 ml/ day) and administration of antihypertensive medication (lysinoprilum 10 mg/ day), diuretics and hypoglycemic medication (metforminum 500 mg twice daily). He was referred to the oncologist for special treatment and follow up.

3. Discussions

About 7% to 15% of all patients with cancer have manifestation of paraneoplastic syndromes [12]. SCLC is the most frequent cancer associated with paraneoplastic syndromes that may be the first manifestation of this neoplasia [1]. Because SCLC is derived from neuroendocrine tissue it expresses peptide and protein factors that are active hormones. These factors clinically manifest as paraneoplastic endocrine syndromes including SIADH and Cushing syndrome (CS) [10].

SIADH is the principal cause of hyponatremia in malignant diseases. In a study conduce by Lyst et al. [9] on 350 patients with SCLC, 11% presented with hyponatremia, however, only 27% of those were symptomatic. Clinical manifestations are due to the water intoxication and hyponatremia. Usually many patients initially presents with fatigue, headache, nausea, and anorexia, which can progress to altered mental status, seizures, coma, and even death. This is depending on the magnitude and chronicity of their hyponatremia.

Laboratory findings in the SIADH production is defined as low serum sodium and a dilute plasma osmolality along with a higher urine osmolality, in the presence of continued urinary sodium excretion [6].

The diagnosis of SIADH cannot be made unless we exclude renal, adrenal, and thyroid dysfunction. Water restriction and demeclocycline are the mainstays of treatment [5]. Water restriction 500-1000 ml/day is indicated to increase serum sodium. In patients with severe symptoms (severe confusion, convulsions, or coma) infusion of hypertonic saline and administration of loop diuretics like furosemide are the treatment of choice.

ACTH is the most commonly produced hormone in lung cancer patients. CS occurs in approximately 1% to 5% of SCLCs [7]. In a retrospective study, 14 of 840 patients with SCLC had ectopic ACTH production [4]. Patients with lung tumor and ectopic ACTH secretion tend to have more extensive disease and more likely to die prematurely [2]. In patients with secretion of ectopic ACTH induced by malign tumor generally present with myopathy, weight loss, hyperpigmentation, electrolyte disturbances rather than typical cushingoid features (buffalo hump, striae) because the hypercortisolism is acute and the patients generally do not survive long enough for morphologic changes to occur. Our patient did not display all of the electrolyte abnormalities generally seen in patients with this syndrome (hypokalemia, metabolic alkalosis).

Glucose intolerance or frank diabetes is typical metabolic disturbance in the ectopic ACTH syndrome. Elevated 24-hour urinary free cortisol level or the lack of suppression of plasma cortisol levels after a 1 mg and 8 mg overnight dexamethasone suppression test is suggested for hypercortisolism and than plasma ACTH levels are measured. In our case midnight cortisol level was 1331 nmol/L with high level of 24-hour urinary cortisol test and further investigation revealed that the patient's cortisol failed to suppress on 1 and 8 mg dexamethasone and then we made a presumptive diagnosis that her tumor lung was secreting ectopic ACTH.

Patients that presented simultaneously with two or more paraneoplastic syndromes were rare. Our patient presented with hyponatremia induced by SIADH as the first sign of a SCLC, which resolved on correct treatment, then further investigations revealed adrenal tumor and manifestation of hypercortisolemia due to ectopic ACTH secretion.

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