

Cushing's Syndrome as a Harbinger of Relapsed Non-Small Cell Lung Cancer

Nadav Sarid MD¹, Esther Osher MD³, Andrea Gat MD², Michael Hoffman MD¹ and Howard S. Oster MD PhD¹

Departments of ¹Internal Medicine A and ²Pathology and ³Institute of Endocrinology, Tel Aviv Sourasky Medical Center affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Paraneoplastic Cushing's syndrome caused by ectopic adrenocorticotropin is common in patients with neuroendocrine tumors such as bronchial carcinoid tumors, small cell lung cancers, medullary carcinoma of thyroid, and pancreatic neuroendocrine tumors [1]. This syndrome is associated with poor clinical outcome and short survival due to a wide range of complications among them opportunistic infections owing to the high levels of cortisol [2]. However, paraneoplastic Cushing's syndrome is rare among non-small cell lung cancer patients, and only about 13 cases have been reported. We describe a case of ectopic Cushing's syndrome associated with adenocarcinoma of the lung. We characterize this entity and present guidelines for high clinical suspicion so that this syndrome may be diagnosed early. This will allow treatment to be initiated as soon as possible.

PATIENT DESCRIPTION

A 51 year old man presented to our hospital due to weakness and hypokalemia. Eight months earlier, he had been diagnosed with stage IIb (T2N1) moderately to poorly differentiated adenocarcinoma of the lung. At that time, glucose and electrolytes were within the normal range. The patient had undergone a left

pneumonectomy and four courses of adjuvant chemotherapy (cisplatinum and navelbine), a standard regimen at that time. Four months prior to admission a PET-computed tomography scan showed no evidence of residual disease. The past medical history was unremarkable apart from smoking.

Upon admission the patient was alert, but appeared tired and his blood pressure was 157/88 mmHg. Physical examination was unremarkable except for decreased breath sounds on the left, the side of the pneumonectomy. There were no cushingoid signs – namely hirsutism, abdominal striae, ecchymoses or hyperpigmentation.

Routine laboratory workup revealed the following: leukocytosis ($17 \times 10^9/L$) with neutrophilia (91.2%), substantial hypokalemia (2.26 mmol/L), elevated fasting glucose (136 mg/dl) and alkalosis (pH 7.54, standard bicarbonate 43.6 mmol/L, base excess 21.1 mmol/L).

Treatment with intravenous and oral potassium chloride failed, raising the suspicion of Cushing's syndrome. Further investigation revealed elevated high morning plasma cortisol ($> 63.44 \mu\text{g}/100 \text{ ml}$, reference range 5–25 $\mu\text{g}/100 \text{ ml}$), and overnight dexamethasone (1 mg) failed to suppress plasma levels of cortisol. Urinary free cortisol was extremely high (12,720 $\mu\text{g}/24 \text{ hr}$, ref. range 9–90), as was the plasma ACTH (843 pg/ml, ref. range 5–46). Spot urine potassium and 24 hour urine potassium levels were within the normal range (46.6 mmol/L and 93 mmol/24 hr respectively, ref. range 20–80 and 26–123 respectively)

ACTH = adrenocorticotropin

but were relatively high given the severe hypokalemia. In light of the above and his history of lung carcinoma, ectopic ACTH secretion was deemed most likely. To identify the source of the ectopic production, a thoracic and abdominal CT scan was performed. The scan demonstrated a small focus in the right lower lobe, an enlarged liver (18 cm diameter) with numerous hypodense foci, and enlarged adrenal glands with a nodular appearance, all enhanced with contrast media. This was compatible with metastatic disease.

Treatment was augmented with angiotensin-converting enzyme inhibitor and ketoconazole. Potassium levels improved considerably (3.49 mmol/L), and the patient was discharged and scheduled for chemotherapy.

One week later the patient was readmitted because of headache, altered mental status and low grade fever. Shortly thereafter a tonic clonic seizure was witnessed. A head CT demonstrated questionable swelling and hypodensity in the upper brainstem, questionable hypodensity in both thalami, and a small enhancing focus in the left central region. Despite treatment he deteriorated quickly and died the following day. Later, a blood culture drawn upon admission grew *Listeria monocytogenes*.

COMMENT

Ectopic ACTH secretion accounts for 9–18% of cases of endogenous Cushing's syndrome. Thoracic carcinoma constitutes 36–46% of these cases, and small cell lung carcinoma 8–20%

[1]. EAS associated with carcinoid tumors often exhibits typical cushingoid features, probably because of the long clinical course. However, typical Cushing's syndrome may be absent or minimal with an EAS that is associated with other tumors, because the onset of this endocrine syndrome may be sudden and appears to coincide with a more aggressive phase of the malignancy.

In one study of EAS in small cell lung carcinoma the most frequent physical findings included edema (83%) and proximal myopathy (61%). Most patients exhibited hypokalemia (96%) and associated metabolic alkalosis. Hyperglycemia was seen in 59% of patients [2]. Markedly elevated ACTH levels are also typical for EAS [1]. The case we describe includes all of these features.

In lieu of a repeat biopsy, the clinical findings (absence of cushingoid features) and laboratory findings (especially profound hypokalemia, and extremely high ACTH level) were highly suggestive of a paraneoplastic EAS despite its rarity in non-small cell lung cancer, and not of pituitary ACTH excess.

EAS is associated with high rates of complications during therapy and short survival. Complications include gastrointestinal ulceration and bleeding, severe infections, particularly, opportunistic ones [2]. In a study of EAS (excluding small cell lung cancer patients) the likelihood of a bacterial or opportunistic infection was highest among patients with extreme hypercortisolism [3].

Ketoconazole, an imidazole derivative, inhibits ergosterol biosynthesis in

EAS = ectopic ACTH secretion

fungi and cholesterol synthesis in mammalian cells. It ameliorates hypokalemia, metabolic alkalosis, diabetes and hypertension in most patients with ectopic ACTH secretion [4]. The ultimate control of EAS is dependent upon successful treatment of the underlying tumor.

In light of this patient's paraneoplastic Cushing's syndrome, the pathology specimen that had been taken from the original lung biopsy 8 months earlier was restained and the neuroendocrine profile (ACTH, chromogranin, synaptophysin stains) was negative. This is not surprising considering that the patient did not have any Cushing's syndrome-related clinical manifestations at that time. In fact, it is characteristic of ectopic ACTH secretion to appear later in the clinical course.

The final clinical and imaging picture was compatible with meningoencephalitis caused by *Listeria monocytogenes*. *Listeria* causes life-threatening infections in the setting of immunosuppression, specifically in the context of EAS [3]. A particular entity caused by *Listeria* is brainstem encephalitis (rhombencephalitis), and some suggest that this constitutes 9% of all central nervous system *Listeria* infections [5]. Clinically, a biphasic presentation is typical: a prodrome that consists of headache, vomiting and fever, followed by the development of symptoms and signs localized to the brainstem (i.e., cranial nerve palsy). Diagnosis of *Listeria* brainstem encephalitis relies on finding lymphocytes or monocytes in the cerebrospinal fluid, blood and CSF cultures; CT scan showing widening of the brainstem with disappearance of the surrounding

CSF = cerebrospinal fluid

cisterns; and magnetic resonance imaging showing a nodular ring-enhancing lesion [5]. The condition is fatal unless treated early with intravenous ampicillin or penicillin.

In summary, we have presented a case of paraneoplastic Cushing's syndrome. It is typical in that it was associated with hypertension, hyperglycemia, severe refractory hypokalemia, and very high ACTH levels, despite the lack of usual cushingoid clinical features. It is unique in that it was associated with non-small cell lung cancer, a tumor type not usually known to secrete ACTH. This case also emphasizes the importance of aggressive therapy to prevent serious and even fatal complications associated with hypercortisolism.

Corresponding author:

Dr. H.S. Oster

Dept. of Internal Medicine A, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel

Phone: (972-3) 697-3366

Fax: (972-3) 697-4855

email: howardo@tasmc.health.gov.il

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Let me never fall into the vulgar mistake of dreaming that I am persecuted whenever I am contradicted

Ralph Waldo Emerson (1803-1882), American writer and philosopher

In science credit goes to the man who convinces the world, not to the man to whom the idea first occurs

Francis Darwin (1848-1925), son of the British naturalist and scientist Charles Darwin. He followed his father into botany