A Case of Paraneoplastic Cushing Syndrome Presenting as Hyperglycemic Hyperosmolar Nonketotic Syndrome

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Abstract
Carcinoid tumors are neuroendocrine tumors that mainly arise in the gastrointestinal tract, lungs, and bronchi. Bronchopulmonary carcinoids have been associated with Cushing syndrome, which results from ectopic adrenocorticotropic hormone (ACTH) secretion. We report the case of a 65-year-old man, a colonel in the US Air Force, with metastatic bronchopulmonary carcinoid tumors treated on a clinical trial who was hospitalized for complaints of increasing thirst, polydipsia, polyuria, weakness, and visual changes. Decompensated hyperglycemia suggested a diagnosis of hyperglycemic hyperosmolar nonketotic syndrome (HHNS). Additional findings, which included hypokalemia, hypernatremia, hypertension, metabolic alkalosis, moon facies, and striae, raised a red flag for an ectopic ACTH syndrome. Elevated ACTH levels confirmed Cushing syndrome. Treatment with a fluid replacement and insulin drip resulted in immediate symptomatic improvement. Cushing syndrome should be considered in carcinoid patients with physical stigmata such as moon facies and
Introduction

Cushing syndrome results from prolonged exposure to excessive glucocorticoids from endogenous or exogenous sources [1]. Exogenous or iatrogenic Cushing syndrome, a consequence of treatment with pharmacologic doses of glucocorticoids for their anti-inflammatory properties [2], is the most common form, followed by endogenous adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas [3]. A very small percentage of cases are the result of nonpituitary or ectopic ACTH secretion from neoplasias such as neuroendocrine tumors, specifically bronchopulmonary carcinoid tumors, accounting for approximately 1% of all the Cushing syndrome patients [4]. The ectopic ACTH production leads to stimulation of the adrenal glands, cortisol hypersecretion, and Cushing syndrome, which commonly features weakness, fatigue, easy bruising, abdominal striae, and hyperglycemia, as in the case of the patient presented below, who was admitted to the hospital with a diagnosis of hyperglycemic hyperosmolar nonketotic syndrome (HHNS).

Distinct from diabetic ketoacidosis, a well-recognized complication in type 1 diabetics, HHNS is an acute hyperglycemic emergency that most commonly occurs in type 2 diabetic patients. Current criteria include marked elevations in blood glucose (>600 mg/dL) and serum osmolarity (>320 mOsm per kg of water [normal = 290 ± 5]), with a pH level >7.30 and mild or absent ketonemia [5]. This report describes a 65-year-old US Air Force colonel with bronchopulmonary carcinoid tumors who presented with clinical signs of HHNS and was diagnosed with paraneoplastic Cushing syndrome due to ectopic ACTH production from the carcinoid tumors.

Case Report

A 56-year-old male patient treated on a clinical trial for bronchopulmonary carcinoid tumors metastatic to the orbit was hospitalized due to complaints of polyuria, polydipsia, weakness, and visual changes. He had experienced polyuria and polydipsia for the past few weeks, and weakness and visual changes over the past few days. One month prior he had been treated for hypertensive urgency with lisinopril and Toprol XL. No previous history of type 2 diabetes mellitus was present. His recent oncology treatment history was significant for focal irradiation of orbital metastases. On admission, his blood pressure was 134/70 mm Hg with a heart rate of 97 beats/min. The rest of the physical examination revealed dry skin, moon face appearance with red cheeks, purple-colored striae on the skin, muscle wasting, and muscle weakness, which was suspicious for Cushing syndrome. A buffalo hump was not present (Fig. 1).

His laboratory examination results were notable for hyperglycemia (venous blood glucose 615 mg/dL) and metabolic alkalosis (pH 7.54; bicarbonate 32.5 mmol/L [normal: 22–26]) without ketonuria. Other values were as follows: glycated hemoglobin (HbA1c) 9.7%; potassium 2.7 mmol/L (normal: 3.5–5.1); sodium 149 mmol/L (normal: 136–145); lactate 4.9 mmol/L (normal: 0.5–2.2), and blood urea nitrogen 23 mg/dL (normal: 7–20). Blood cultures and urinalysis were negative for evidence of infection. No EKG abnormalities were present.
Based on these clinical and laboratory findings, the patient was diagnosed with HHNS. Following intravenous hydration, potassium replacement, and regular insulin infusion (0.1 IU/kg/h), the patient reported immediate symptomatic improvement. On suspicion of Cushing syndrome, an endocrine workup was started, which included measurement of serum cortisol and plasma ACTH. The values were as follows: serum cortisol 40.5 mg/dL (8:00 a.m.; normal: 5–25) and plasma ACTH 112.3 pg/mL (normal: 7.2–63.3), confirming the diagnosis of Cushing syndrome. It is unclear whether the emergence of Cushing syndrome represents active secretion of ACTH from the tumor due to disease progression, although a recent CT scan showed stable disease with central tumor necrosis. A more intriguing possibility is that the ACTH contained within the tumor was passively released, i.e., liberated into the circulation from dead or dying neuroendocrine cells due to recent irradiation of the patient’s orbital metastases.

**Conclusion**

The pathology of ectopic or paraneoplastic Cushing syndrome is mediated by ACTH, stimulating the adrenal cortex to produce cortisol, which, in turn, stimulates proteolysis [6] and inhibits protein synthesis, leading to muscle wasting cross-reactions, and activates the mineralocorticoid receptor [7], which then stimulates renal potassium and renal proton excretion as well as renal sodium absorption (leading to hypokalemia, metabolic alkalosis, and hypertension, respectively) and induces insulin resistance in peripheral tissues [8] (mainly muscles and gluconeogenesis), leading to diabetes mellitus. Hypercortisolism in this patient led to the development of a hyperosmolar hyperglycemic nonketotic state, a hallmark of type 2 diabetes mellitus. Aside from curative resection – which was and is impossible in this patient's case, due to the number of metastases – treatment options include ketoconazole and octreotide to inhibit steroid synthesis and a switch to cytotoxic chemotherapy (platinum doublets), which is permitted in the context of the clinical trial.

Paraneoplastic syndromes are estimated to affect up to 8% of patients with cancer [9], which is not exactly rare per se, but since each individual syndrome only occurs in a minority of patients, few clinical guidelines are available. For this reason, a high index of clinical suspicion is important for early diagnosis and prompt management to improve outcomes both for established and for undiagnosed cancer patients, since a paraneoplastic syndrome may be the first sign of malignant disease.

On the basis of this case report, a paraneoplastic Cushing syndrome should be considered in the differential diagnosis of patients who present with new-onset diabetes and HHNS in the context of physical stigmata and biochemical abnormalities (i.e., hypokalemia and metabolic alkalosis) suggestive of hypercortisolism.

**Statement of Ethics**

The authors have no ethical conflicts to disclose.

**Disclosure Statement**

The authors have no conflicts of interest to declare.
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Fig. 1. Appearance and symptoms of the patient on admission.