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Case Report

Pure Androgen-Secreting Adrenocortical Carcinoma Presenting with Hypoglycemia

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Abstract

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy. Most patients present with steroid hormone excess or abdominal mass effect. Pure androgen-secreting ACCs are rare, while hypoglycemia is an unusual presentation of this malignancy. We present a 26-year-old woman with hypoglycemia and history of adrenalectomy due to a large adrenal mass which was diagnosed as nonfunctional adrenal adenoma. She was admitted in our hospital 10 days after her fetal loss with repeated episodes of severe hypoglycemia. She had a high serum dehydroepiandrosterone sulfate (DHEA-S) and her hypoglycemia was associated with low insulin and C-peptide levels. Imaging revealed liver metastasis and immunohistochemical studies of the biopsied lesions confirmed the diagnosis of ACC.

Keywords: Adrenocortical carcinoma, C-peptide, DHEA-S, Hypoglycemia, Insulin

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Introduction

Non-islet cell tumor hypoglycemia (NICTH) is a serious and rare paraneoplastic manifestation of malignant tumors.[1,2] It is four times less common than insulinoma[2] and tumor production of insulin-like growth factor II (IGF-II) is considered as its major cause.[3-5] In a review of this topic, de Groot et al reported solid tumors of mesenchymal and epithelial origin as the main culprits for this complication.[1] Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with an estimated annual incidence of 0.5–2 per million population, slightly more prevalent among women (F/M ratio: 1.5/1).[1]

Affected patients tend to have a poor prognosis, with an average 5-year survival rate of 32%–45%.[6] Sixty percent of ACCs are hormonally active; Cushing's syndrome, with or without simultaneous androgen overproduction, constitutes the most common hormonal excess syndrome.[1,7] However, pure androgen-secreting ACCs are rare and NICTH is extremely rare in cases of adrenal carcinoma.[8,9] Here, we present the first case of a pure androgen-secreting ACC who presented with hypoglycemia, one year after adrenalectomy.

Case Report

A 26-year old woman was referred to our hospital for evaluation and management of episodic severe hypoglycemia manifesting as episodes of decreased level of consciousness (LOC), particularly in the morning.

Her past medical history was remarkable for gradual left-sided flank pain and bulging about 1.5 years ago. Her evaluation had revealed a large non-functional left adrenal mass (17 × 15 × 13 cm). Therefore, she had undergone adrenalectomy about 1 year ago and histopathological evaluation of the aforementioned mass was reported as adrenal adenoma.

The patient was relatively well and experienced gradually increasing hirsutism. She became pregnant about 4 months prior to the current hospital admission. Her fetus was lost about 10 days prior to hospitalization, when episodes of decreased LOC started and low plasma glucose was detected. She looked well and had severe hirsutism without Cushingoid appearance. Her vital signs included a blood pressure of 130/86 mm Hg, pulse rate of 73/min, and respiratory rate of 18/min. Abdominal examination detected hepatomegaly. Paraclinical investigations revealed suppressed insulin, C-peptide, and IGF-I levels during hypoglycemic episodes. Insulin antibodies were not detected in the patient. She had low serum potassium while her serum aldosterone was normal. Pheochromocytoma and hypercortisolism were ruled out, but serum DHEA-S level was elevated (Tables 1 and 2).

During hospitalization, she had frequent episodes of symptomatic hypoglycemia, which required continuous hypertonic glucose infusion. Computed tomography of the

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Table 1. Laboratory Blood Test Results of the Patient

	The Patient	Normal Range
Fasting glucose (mg/dL)	20	80–100
Fasting insulin (mIU/L)	2.8	<3
C-peptide (ng/mL)	0.37	0.8–3.1
IGF-I (ng/mL)	49	117–329
DHEA-S (µg/mL)	12.5	0.65–3.8
ACTH (pg/mL)	10.2	8.3–57.8
Potassium (meq/L)	3.3	3.5–5
Lactate dehydrogenase (U/L)	1740	140–280
Alpha fetoprotein (ng/mL)	2.8	0.89–8.78
Cancer antigen19-9 (U/mL)	18	<35
Carcinoembryonic antigen (ng/mL)	1.8	<5

IGF-I, Insulin-like growth factor one; DHEA-S, dehydroepiandrosterone sulfate; ACTH, adrenocorticotropic hormone.

Table 2. 24-Hour Urinary Catecholamines and Free Cortisol Levels of the Patient

	The Patient	Normal Range
VMA (mg/d)	9.5	3–13
Metanephrine (µg/d)	158.6	<350
Normetanephrine (µg/d)	302	<350
Free cortisol (µg/d)	171	4.3–176

abdomen revealed an enlarged liver with multiple lesions, suggestive of metastasis (Figure 1). CT-guided biopsy of the mentioned lesions was performed. Immunohistochemical study of the specimens was positive for alpha inhibin and Melan-A and 45% proliferative activity was determined in Ki67 staining (Figure 2). Based on these findings, a pathological diagnosis of metastatic ACC was made. She received adjuvant mitotane treatment and experienced no further significant hypoglycemic episodes. The patient was considered for additional combined chemotherapy, but she died a few months later.

Discussion

NICTH is rare and hypoglycemia can be the first manifestation of a neoplasm. In this regard, Fukuda et al reported hypoglycemia as the initial sign of a tumor in 48% of their cases; among their patients, 13% had a tumor resected in the past without any evidence of hypoglycemia at that time, similar to our case.[4] Sisman et al also reported a patient with ACC whose primary tumor was non-functional, while its local recurrence after operation led to hypercortisolism.[10]

The most important mechanism of NICTH has been attributed to increased glucose utilization and inhibition of glucose production in the liver due to tumoral secretion of incompletely processed IGF-II, the so-called big IGF-II. Furthermore, less common causes include expression of autoantibodies against insulin or its receptors and

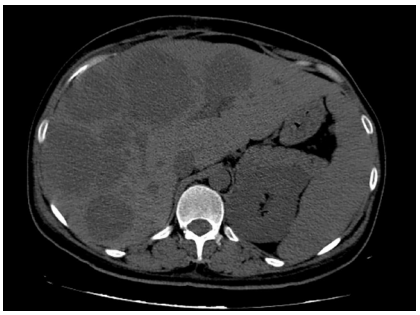

Figure 1. Abdominal Computed Tomography Demonstrating Multiple Well-Defined Hypervascular and Heterogeneously Enhanced Lesions up to 12.5 × 8.8 cm Throughout the Liver.

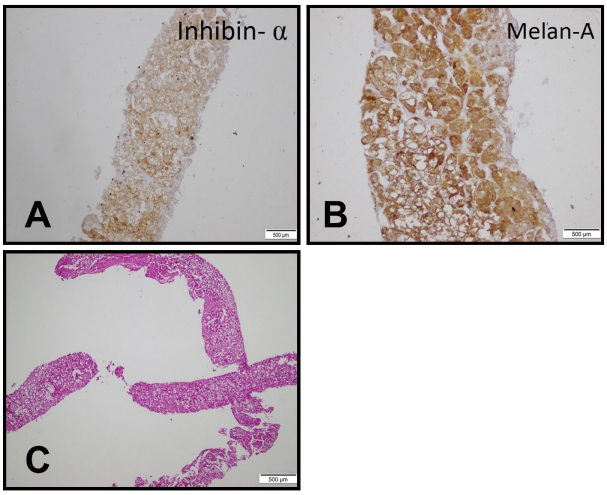

Figure 2. Figure 2. Immunohistochemical (IHC) and histological (C, H&E, x40) evaluation of tru-cut liver biopsy confirmed metastatic adrenocortical carcinoma by positivity of inhibin-α (A, IHC, x100) and Melan-A (B, IHC, x400).

tumor production of glucagon-like peptide 1, or rarely, IGF-I.[11-13] Indeed, in 70% of patients, overexpression of big IGF-II is the primary mediator of hypoglycemia.[3,5] It should be noted that in clinical settings, serum levels of total IGF-II are not always elevated and assays for big IGF-II are not commercially available.[3] Big IGF-II has greater bioavailability to the tissues and inhibits IGF-I production.[5] Therefore, in the absence of IGF-II assays, suppressed serum insulin in combination with low IGF-I levels at the time of hypoglycemia may be helpful to establish a diagnosis of NICTH. In this regard, high serum IGF-II/IGF-I ratio (>10) has been reported useful for diagnosis of IGF-II-producing NICTH.[3] In a review of 28 patients with NICTH, Zapf et al reported elevated big IGF-II, but reduced normal IGF-II concentrations in 25 cases.[14] Hypokalemia may also accompany IGF-II-secreting tumors, secondary to the insulin-like activity of big IGF-II.[4]

ACC is a rare and aggressive tumor. Most patients present with syndromes secondary to steroid hormone excess, mostly hypercortisolism, with pure androgen-

secreting adrenal carcinomas comprising less than 10% of the secretory ACCs.[8] In one of the largest series over a period of 33 years, Moreno et al reported 21 patients with pure androgen-secreting adrenal tumors.[9]

ACC might be a rare potential candidate causing NICTH through incomplete processing of IGF-II.[15] To our knowledge, fewer than 10 cases of NICTH accompanied by ACC were recognized in a PubMed search from 1984 onward. The natural clinical course of ACC is not well known because of its poor prognosis and short survival, but its risk increases with tumor size. Of note, histologic differentiation of benign and malignant neoplasms arising from the adrenal glands is difficult.[2,10] To overcome this problem, immunohistochemical (IHC) markers have been used in recent years and the expression of Ki67 (>10%) has been considered a malignant feature of adrenocortical tumors.[2,16] Unfortunately, we could not measure the IGF-II level in our patient, but she had suppressed IGF-I and insulin levels. However, measurement of total IGF-II may not be helpful because it cannot distinguish the big IGF-II, and its normal level does not rule out NICTH.[3,17] Also, pregnancy is uncommon in patients with functional adrenal tumors, because hyperandrogenism and/or hypercortisolism are associated with menstrual disturbances. Our patient became pregnant and androgen excess did not interfere with her conception. In this regard, Morris et al also described virilization of a 46 XX female infant by a maternal large cortisol and androgen-secreting ACC.[18]

For NICTH, surgical resection of the tumor is the best treatment and the metabolic alterations are reversible after successful surgery.[17] However, recurrence and metastasis are common even after complete resection of the ACC. Adjuvant treatment with mitotane has shown positive effects on survival, although chemotherapy and radiotherapy do not significantly affect disease-free survival.[7,16]

To our knowledge, this patient is the first reported case who experienced two rare presentations of ACC simultaneously.

In conclusion, the possibility of NICTH should be considered in non-diabetic subjects with recurrent hypoglycemia in the presence of low serum insulin, C-peptide, and IGF-I levels. We have reported the first case of a pure androgen-secreting adrenal carcinoma associated with NICTH, manifesting one year after adrenalectomy. Although very rare, ACC should be kept in mind as a differential diagnosis in cases with hypoglycemia and current or past history of an adrenal mass.

Authors' Contribution

FK; Design, data analysis and interpretation and writing. AD; Pathology data gathering and interpretation. MF; Data collection. BD; Drafting the manuscript. All authors read the manuscript and approved its final version.

Conflict of Interest Disclosures

The authors declare no conflicts of interest.

Ethical Statement

An informed consent was obtained from the patient and the patient name was kept concealed.

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