Case Report

Ectopic Cushing's syndrome Of Unknown Origin: A Rare Case Report

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Abstract

Background: Cushing's syndrome is a rare disease caused by excessive secretion of cortisol by adrenal cortex (hypercortisolism). Bilateral adrenal hyperplasia due to increased secretion of adrenocorticotropic hormone (ACTH) by pituitary gland is usually known as the main cause of Cushing's syndrome. The 5-year survival rate for patient with Cushing's syndrome is approximately 50% unless associated with treatment. Etiologic diagnosis therefore plays an important role in prompt treatment. The purpose of this study is to inspect a Cushing's syndrome with unknown cause.

Case presentation: A 36-year-old married man with complaint of periorbital and upper trunk swelling (with no buffalo hump) and lower extremity weakness presented to doctor's clinic. He also had a one-year history of blurred vision, hypertension, facial and periorbital edema and difficulty getting up from a sitting. After physical examinations and laboratory testing, diagnosis of Cushing's disease with unknown cause was made and surgical removal of both adrenal glands was suggested. He underwent bilateral adrenalectomy in two separate operations and his symptoms gradually reduced during the next months.

Conclusion: According to this study and other same case report studies conducted, surgical removal of adrenal gland is the most effective treatment if the patient does not respond to medication. Even if the cause of Cushing's disease is not known, like the case mentioned.

Keywords: Cushing's syndrome, Adrenocorticotropic hormone, hypercortisolism

Introduction

Cushing's syndrome is caused by high production of cortisol (and other Glucocorticoids hormones) by the adrenal cortex. It is mainly due to bilateral adrenal hyperplasia resulted from high secretion of Adrenocorticotropic hormone (ACTH) from the pituitary gland (1-3). If untreated, only 50% of patients with Cushing's syndrome are likely to survive for up to 5 years.A Cushing's syndrome induced by corticosteroid treatments is the most common form of this disease. Cushing's disease is extremely rare that a Danish study stated that its incidence is less than one case

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per million a year (4). However, asymptomatic micro-adenoma (in sizes below 10mm) from the pituitary gland has been reported in approximately one in every six patients with Cushing's syndrome (5).

Endogenous causes of this disease is more common in women than men and excessive secretion of ACTH is thought to be the main cause associated with more than 80% of incidents. From all the cases, 80% are related to pituitary adenoma and 20% are due to adrenal glands' excessive secretion (6). Due to the various mentioned causes of Cushing's syndrome including adrenal hyperplasia, adenoma or corticosteroid therapy, it may become challenging to find the exact origin of this disease which affects the treatment process, therefore we aimed to present a rare case of Cushing's syndrome with an unknown etiology.

Case presentation

A 36-years-old married male teacher was referred to the doctor's office with complaints of edema around the eyes and upper body (without Buffalo neck) and lower extremity weakness. During the last year prior to his visit, he was experiencing blurred vision, increased blood pressure, swelling of the face and around the eyes, lower extremity weakness at the time of getting up from the ground. The patient did not have productive coughs, was not a smoker and did not mention a history of a specific disease.

During the initial examination, bruising of nails, facial edema, facial skin darkening and increased fat in supraclavicular area without Buffalo shaped neck, edema of lower extremities, easy bruising and darkening of Knuckles (the skin area PIP and DIP fingers) were observed. Chest examination and abdomen were normal, patient's blood pressure was 118/166 mmHg, pulse rate 84 and weight of 86 kg were recorded.The serum cortisol levels not only did not decline after testing with high-dose of dexamethasone but increased from 23 to 50mg/dl.Pulmonary and abdominal CT scan results were normal and the scan without electrolyte was reported as negative. Prescriptions included 50 mg of Spironolactone in the morning and evening along with 200 mg of Ketoconazole twice a day. The patient was recommended to undergo bilateral adrenal surgery (with diagnosis of unknown origin ectopic Cushing).According to the surgeon's report, due to adhesion of left adrenal gland to the kidney during the operation, both left adrenal gland and kidney were removed and right adrenal surgery was postponed to another time. Patient's edema was reduced after surgery while patient remained lethargic. A 10% solution of oral potassium chloride and 50mg Losartan was administered 2 times a day. Patient complained of sweating following feeding.Postsurgical tests are shown in Table 3

Complete resection of right adrenal gland was recommended but the patient did not comply. The patient attended a month later while 24h cortisol was altered to 58 in the normal range and the amount of ACTH was 81.7. The patient was once more referred a month later with complaints of edema and high blood pressure. Blood pressure was reported as 158/106 mmHg and pulse rate

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was recorded as 80. UFC was reported at more than 1,000 micrograms/day and ACTH was 190. The patient was presented to surgery afterwards. Postsurgical test showed that UFC levels were reduced to 4.5 micrograms per day while plasma cortisol was 0.52 mg/dl and ACTH was 126 following the removal of right adrenal gland. The patient was treated with 7.5 mg daily prednisolone and 100 mcg daily Fludrocortisone. The patient's symptoms were improved in the next reference. At least two screening tests are required for the diagnosis of Cushing's syndrome.

After the diagnosis of Cushing's syndrome, first, serum levels of ACTH were check to differentiate the two types of ACTH dependent and ACTH independent Cushing's syndromes. In case of ACTH dependent, MRI of the pituitary gland should be performed. If the adenoma was detected at 6mm, the patient is diagnosed with ACTH-secreting adenoma and surgery should be performed. If detected ACTH were low, adrenal imaging should be performed. In cases of high ACTH and adenoma's absence in MRI or adenoma lower than 6mm, inferior petrosal sinus biopsy should be performed for definitive diagnosis in order to determine whether the ACTH-secreting masses are from pituitary gland or secreted from an ectopic tumor e.g. lung carcinoid. CT scan, MRI and PET are used for the diagnosis of misplaced ectopic Cushing syndrome (11). Screening tests were initially performed on this patient. Urinary cortisol was very high so the diagnosis was definitive. Patient's serum was high therefore ACTH-Dependence was argued. Since pituitary MRI was normal, the patients had to be IPSS which was not possible. Pulmonary, abdominal, neck CT scans were normal and the patient with diagnosis of ectopic Cushing syndrome had to go under bilateral adrenal gland resection.

Discussion:

Cushing's syndrome is an extremely rare disease. A Danish study has reported the incidence of this disease as less than one case in a million per year (4). In Manshouri et al. case report in 1391, titled *Ectopic Cushing syndrome with mesenteric neuroendocrine tumor etiology*, a 62 years old female with Cushing symptoms and a new type of diabetes with a history of peptic ulcer was referred to Imam Khomeini Hospital in Tehran. Exogenous Cushing's syndrome was initially thought therefore administration of prednisolone was stopped. Symptoms were uncontrollable and the patient went under surgery (resection of mesenteric tumor, liver metastases and bilateral adrenalectomy). A year after the diagnosis, a tumor and multiple metastases in both lobes of the liver were found and the patient was finally diagnosed with NET. Hormone replacement therapy of adrenal gland decreased ACTH and cortisol levels after surgery and a year later normal and non-specific symptoms were reported (9). In our study the removal of bilateral adrenal glands was also the definitive treatment.In another case report from Alcántara et al. in 1392 in the USA, titled *a rare case of Cushing's syndrome due to ectopic adrenocortical hormone secretion*, a 26 years old woman due to ACC of sublingual salivary gland and pulmonary metastasis were treated with a single sign of painful

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mass in the uterine cervix. Treatments and surgery were performed in 3 consecutive periods which ultimately did not have any results. Two months after the end of final treatment period, symptoms of insomnia, lower extremity weakness, amenorrhea, acne, hyperpigmentation, glucose intolerance, and 4 kg weight gain had emerged. 24-hour urine test indicated high levels of cortisol in the patient. During further investigations, hypokalemia and metabolic alkalosis, hyper-cortisol and ACTH levels were found which were not suppressed with 8mg of dexamethasone. Pituitary MRI was normal and then drug therapy began which was unsuccessful.

This confirms that in people with cancer of the salivary glands which can lead to FAS, or in people with hypertension, hypokalemia and metabolic alkalosis and glucose intolerance when drug therapy is irresponsive, the best recommendation for treatment is the removal of both adrenal glands. In this case also, the symptoms decreased and the patient shifted towards recovery after the removal of adrenal glands (7) which corresponds with the treatment procedures performed in our study.But the most significant difference between our case with all other studies is that the origin of this disease in our patient remained unknown. This made the treatment process difficult at first, but eventually the patient recovered completely by removing adrenal glands. This case has not been yet reported by other studies.

Conclusion:Based on our case report and other similar studies by Manshouri and Alcántara, the best treatment choice is the removal of adrenal glands in cases when patients do not respond to drug therapy, even in similar cases to our study where the patient is diagnosed with Cushing's syndrome of unknown origin.

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Table 1. Laboratory tests are shown in Table 1

UFC: CORTISOL	1152 µg/day
ACTA=12Pituitay met	NL

Table 2. 24-hour urine catecholamine was normal. Test results are reported in Table 2.

Test name	Normal range	Conclusion
IGF1		Normal
PTH		80
FBS	70_100	Normal
Creatinine	0.2_1 mg/dl	Normal
25(OH)D	30_100 mg/ml	12.3
AIT	<30	95
LH	10	2.5
FSH	10	5.3
Na	35_155	143
TESTOSTERON	2_10	1.5

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BMD		Osteopenia
Serum Cortisol	5_20	39 (8 a.m)
Serum Cortisol	10_60	38 (16 p.m)

Table 3. Postsurgical tests in

Test name	Normal ranges	Conclusion
Blood Pressure	<130/dc	111/88
k	3.5_5	4.5
Na	35_155	139
TG	40-150	232
Ca	8.5_10.5 mg/dL	8.3
UFC		14175 mg/g
NCV	80_90	92
ACTH	10_60	96 pg/nv
cortisol	5_25	25µg/dl

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