

EVALUATION OF A HYPERCORTISOLISM CASE

Murat SUHER, M.D., Nuri ÇAKIR, M.D., Metin ARSLAN, M.D.,
Burçak KAYHAN, M.D., Göksun AYVAZ, M.D.

Gazi University, Faculty of Medicine, Department of Endocrinology and Metabolism,
Ankara, Turkey
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SUMMARY : *Though all investigations were made for the case of hypercortisolism, we couldn't be able to find the etiology of the illness. In our case, all data were in favour of Cushing's disease, but we could eliminate wholly neither Cushing syndrome nor ectopic ACTH producing tumor.*

Key Words : *Hypercortisolism, Cushing Disease.*

INTRODUCTION

Hypercortisolism could be due to both hypothalamic and pituitary adenom (75-90 %), adrenal neoplasm (15-19 %) or ectopic ACTH producing tumor (5-15 %) (3, 4, 5, 14).

Despite hypercortisolism was diagnosed by the clinical and laboratory findings, we couldn't find the localization for etiopathogenesis. Sometimes it could be very difficult to find the etiologic cause.

In this case report, we discussed about a hypercortisolism case that we couldn't identify any localization for pathology.

CASE REPORT

A 25 years old woman complained of hirsutismus, central obesity with rounded face and menstrual disorders. Because of Verruco plantaris she had used alpha-2 interferon for a month 1 year ago. In her family history her uncle had NIDDM.

In physical examination, height : 1.52 m, weight : 52 kg, body mass index : 23.5, blood pressure : 120/80 mmHg, pulse rate : 88 / min rhythmic. She

had moon face and facial plethora. The extremities were thin. According to the Ferriman-Gallwey hirsutismus score, the upper lip : 2, the chin : 3, the chest : 0, the abdomen : 0, the back : 2, the sacroiliac region : 2, the upper sides of the extremities : 0, the lower sides of the extremities : 1. In laboratory findings total urine examination was normal. Hb : 13.4 gr, red blood cells : 4310000, white blood cells : 7750, thrombocytes : 238000, Htc : 40.8 %, peripheral blood smear : Neutrophils : 74 %, Monocytes : 7 %, Lymphocytes : 19 %. BUN : 17 mg/dL, fasting blood glucose : 65 mg/dL, Na : 139 mEq/L, K : 3.9 mEq/L, alkalen phosphatase : 88 U, AST : 21 U, ALT : 25 U, total proteins : 6 gr, albumin : 3.7 gr, GGT : 19 U, total lipids : 868 mg, cholesterol : 250 mg, creatine : 0.9 mg, Ca : 8.4 mg, P : 4.2 mg, uric acid : 5.1 mg, Cl : 112 mg. E.C.G, O.G.T.T, thorax graphy and sella graphy are all normal.

Plasma cortisol : 54-52, 26 µg/dl at 8 A.M, 32,47-25,79 µg/dl at 11 P.M, 24 hours urine free cortisol : 590 ngr (22-90), 1 mg dexamethasone suppression test : plasma cortisol level is 40.29 µg/dl, 2 mg dexamethasone suppression test : basal plasma cortisol level is 21.35 µg/dl (A.M), 25.59

µgr/dl (P.M), second day plasma cortisol level is 33.6 µgr/dl. Urinary free cortisol levels first day : 250 µgr/dl, second day : 230 µgr/dl.

8 mg dexamethasone suppression test : basal plasma cortisol level is 22.12 µgr/dl, urinary free cortisol : 1015 µgr/dl, second day plasma cortisol level is 9.17 µgr/dl, urinary free cortisol level first day : 225 µgr/dl, second day : 70 µgr/dl.

Adrenal CT, thorax CT, abdominal ultrasound, thyroid ultrasound, gynecologic ultrasound, pituitary CT and NMR are all normal. Bone mineral density is in accordance with osteoporosis : L 1 : 74.3 (N : 120), L 2 : 74.3 (N : 120), L 3 : 68.7 (N : 120), L 4 : 79.3 (N : 120).

In the octreotid scan, there wasn't established any somatostatin receptors which conformed with metastasis.

ACTH venous sampling from the inferior petrosal sinus after CRH stimulation test :

DISCUSSION

In our case the diagnosis of hypercortisolism was supported by the positive findings of physical examination, elevated levels of either plasma cortisol or 24 hours of urinary free cortisol, and negative suppression with 1 or 2 mg dexamethasone suppression test (3, 4, 5, 14).

Hypercortisolism could be due to a hypothalamopituitary adenoma (75-90 %) or adrenal tumor (15-19 %) or ectopic ACTH producing tumor (5-15 %) (3, 4, 5, 14).

Our case didn't have adrenal tumor because the blood ACTH levels were in the normal limits. It had to be under 20 in adrenal adenomas and carcinomas (3, 4, 14, 16). We thought that in this case hypercortisolism depended on the hypothalamopituitary adenoma or ectopic ACTH producing tumor. The pituitary adenoma caused 75-90 % of hypercortisolism. In the pituitary adenoma, male/female ratio is 8/1 and half of the case ages were between 20 and 40

Blood	Peripheral venous sampling	Right pituitary venous sampling	Left pituitary venous sampling	Plasma sampling
0'	25 pg/ml	40 pg/ml	50 pg/ml	-
	50 pg/ml	35 pg/ml	40 pg/ml	21.73 Mgr/ml
15'	-	15 pg/ml	35 pg/ml	22.87 Mgr/ml
30'	70 pg/ml	30 pg/ml	35 pg/ml	30.01 Mgr/ml
60'	30 pg/ml	20 pg/ml	20 pg/ml	29.01 Mgr/ml
90'	80 pg/ml	25 pg/ml	22 pg/ml	40.06 Mgr/ml

ACTH Stimulation Test :

Basal plasma cortisol level; 21.34 (A.M), 29.40 (P.M) Basal urinary free cortisol in 24 hours: 225 ngr.

First day plasma cortisol; > 65 Mgr/dl, Urinary free cortisol in 24 hours : 1995 ngr

Second day plasma cortisol; > 65 Mgr/dl, Urinary free cortisol in 24 hours : 2020 ngr

Third day plasma cortisol; > 65 Mgr/dl, Urinary free cortisol in 24 hours : 2380 ngr

Fourth day plasma cortisol; > 65 Mgr/dl, Urinary free cortisol in 24 hours : 2465 ngr

Other Hormones : TT3 : 0.8 ng/ml, TT4 : 7.14 ng/ml, FT4 : 1.14 ng/ml, FT3 : 1.85 ng/ml, TSH : 0.56 m IU/ml, beta-hCG : 6 m IU/ml, FSH : 13.25 m IU/ml, LH : 6.03 m IU/ml, E2 : 22.78 pg/ml, free testosterone : 2.55 pg/ml, DHEA-S : 3850.57 ng/ml, progesteron : 0.91 ng/ml, prolactin : 8.41 ng/ml.

years old. All of these findings were suitable for our case (4).

Plasma ACTH levels changes between 40 and 200 U in Cushing disease (3, 4, 5, 14, 16).

The ACTH level was in normal range in our case which supported the diagnosis of Cushing's disease. Some ectopic ACTH producing tumor's blood

ACTH levels could be the same as Cushing disease.

Malorkey and Zvara showed that gamma interferon increased the production of ACTH in Cushing disease (9). But in our case, alpha interferon was used and so, it didn't have any relation with ACTH level.

Occult ectopic ACTH producing tumor's causes are bronchial adenoma, carcinoid tumors, pancreas islet cell tumors, thyroid medullar carcinomas, pheochromocytomas and thymomas (4, 5, 15).

The sensitivity of thorax graphy was 30 % and thorax CT imaging was 89 % for ectopic ACTH producing tumors which arises from lung (5). While in our case thorax graphy, thorax CT and pancreas CT were all normal, so at all they didn't support the diagnosis of bronchiolar and pancreas Langerhans cell tumors. The liver was normal in abdominal ultrasound and the level of 24 hours urine 5-HIAA was in normal range. Because of these findings, we didn't think carcinoid tumor in this case. There wasn't any conformity with thyroid medullar carcinoma in ultrasound and in physical examination. For these reasons, we didn't think for ectopic ACTH producing tumor. Although our suspects continued, we didn't determine any adenoma in pituitary. On the other hand, most of the ACTH producing tumors were under the level of 10 mm. The other 50 % were under the level of 55 mm (4). Pituitary adenomas were determined at the rate of 50-60 % in sella CT (4, 5, 12, 13). In an other report, 22 Cushing's diseases were diagnosed by CT (13). This could also show the sensitivity of CT in pituitary adenomas, which was about 50 %. In the other report, 5 cases of 20 Cushing's diseases were diagnosed by CT (10). Cella NMR imaging sensitivity was 71 % and the specificity was about 87 % for pituitary adenomas (4).

As the tumor was too small, sella CT and NMR did not determine pituitary adenoma in our case. The suppression of 8 mg dexamethasone test supports the diagnosis of Cushing's disease (3, 4, 5, 14). On the other hand, 15-25 % of ectopic ACTH producing tumor suppression could be obtained by 8 mg dexamethasone (6, 11, 16).

Although our case was in favour of Cushing's disease because of the suppression tests, ectopic ACTH producing tumor was still suspected. Therefore, ACTH sampling from the inferior petrosal sinus was used to demonstrate the difference between pituitary adenoma and ectopic ACTH producing

tumor. If the petrosal sinus ACTH level was 1.8-2.5 times higher than the peripheral level, this could be a strong indication for a pituitary adenoma. In our case, we determined that the difference gradient between the left petrosal sinus venous ACTH level and peripheral venous ACTH level was 2 times. This difference was in favour of Cushing's disease. In the other report, the petrosal sinus ACTH level was 2 times more than peripheral ACTH level in 205 of 215 Cushing diseases. So, the petrosal sinus ACTH sampling sensitivity was 95.3 %. In another report, the highest gradient of petrosal sinus sampling of 4 Cushing disease cases were determined 1.4 who were diagnosed before measuring sinus ACTH sampling (13). Petrosal sinus ACTH gradient could be more than peripheral ACTH gradient in pituitary adenomas but this gradient difference couldn't be true, if pituitary adenoma's hypersecretion was intermittent or the catheter's localization was wrong (13). In the reports, the rate of petrosal sinus ACTH gradient to the peripheral ACTH gradient was 0.9-1.6 in ectopic ACTH producing tumors (13). Between the right and left petrosal sinuses ACTH gradient was 1.4 or more. This ratio could show us the localization of tumor (2, 11). But, this was true in the rate of 70-85 % in the cases (2, 12, 13). Also we couldn't show any lateralization between 4-6 mm dimensions tumors (15).

All these data show us that our diagnosis confirmed with Cushing disease but we couldn't separate exactly from ectopic ACTH producing tumors. Petrosal sinus sampling test didn't distinguish the occult ectopic ACTH producing tumor from small pituitary adenoma. For this reason, we could use CRH stimulation test. Under normal conditions, both plasma ACTH and cortisol increased 2 times in pituitary adenoma by CRH stimulation test (3, 5, 16). In another report suggested that, if plasma cortisol increased 20 %, we could eliminate the diagnosis of ectopic ACTH producing tumor (15). In the other report, when plasma cortisol increased 60 % after CRH stimulation test, it would give the positive response of the test. On the other hand, in 193 of 203 cases plasma cortisol increased 50 % in petrosal sinus sampling after CRH stimulation test (12).

Our case's plasma cortisol increased by the rate of 80 % after CRH stimulation test so this supported the diagnosis of Cushing's disease. However the case of Cushing's disease couldn't have responded the CRH stimulation in the rate of 5 % (6). Although our case was a Cushing's disease, there was a lack of

rise in ACTH, after CRH stimulation test. It was reported that, CRH stimulation test's sensitivity was 86 %, and specificity was 100 % for Cushing disease (12). In one study, a case had Cushing disease whose petrosal sinus ACTH level in CRH stimulation test rose by the rate of 1.3. At the same study, plasma ACTH level was greater than petrosal sinus ACTH level in the other Cushing's disease (13).

In our case, a gradient of 2.3 was obtained between the right and left petrosal sinuses at 15th minute without rising in petrosal sinus ACTH level by the CRH stimulation test. Peripheral ACTH level was measured higher than petrosal sinus ACTH level (13).

In published reports, 22 cases who had Cushing disease, were applied CRH stimulation test. In 7 plasma ACTH and cortisol levels didn't increase. According to these reports, it was possible to have a response to the CRH stimulation test (13). So that, we couldn't eliminate the diagnosis of Cushing disease in our case, though her petrosal sinus ACTH didn't rise by CRH stimulation test. It was in favour of Cushing disease when both plasma cortisol and urine free cortisol rose in ACTH stimulation test (4, 5, 16). ACTH Stimulation test responds confirmed with Cushing disease in our case.

Although all of these data were in favour of Cushing's disease, we couldn't eliminate ectopic ACTH producing tumor. Somatostatin uptake test was higher at this kind of tumors which had somatostatin receptors (1, 7, 8). When we examined somatostatin receptors by Indium 111, the test did not establish any pathologic area in our case. So we eliminated the diagnosis of ectopic ACTH producing tumors.

Although, we couldn't determine any pituitary adenoma with all of these clinical and laboratory examinations, we thought that she had Cushing's disease. Thus, we began to ketoconazole therapy. As a result; while the etiology of hypercortisolism wasn't determined, this condition couldn't eliminate the diagnosis of Cushing's disease.

Correspondence to : Dr.Murat SUHER
Gazi Üniversitesi Tıp Fakültesi
Endokrinoloji ve Metabolizma
Anabilim Dalı
Beşevler
06510 ANKARA - TÜRKİYE
Phone : 312 - 214 10 00 / 5819

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