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ECTOPIC ACTH SECRETION AND CUSHING'S SYNDROME

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SUMMARY - Ectopic ACTH secretion was the first paraneoplastic endocrine syndrome described in the literature. The most common tumors associated with ectopic ACTH production are small-cell lung cancer and atypical carcinoids. High cortisol levels have also been described in patients with adenocarcinoma and large-cell carcinoma of the lung, other carcinoid tumors, thymoma, neural crest tumors, medullary carcinoma of the thyroid, and bronchial adenomas. Patients rarely live long enough for frank Cushing's syndrome to develop. A 30-year-old male is described, who was admitted to endocrinology ward for clinical features of Cushing's syndrome. Outpatient examination showed high levels of plasma cortisol on several occasions, without suppression of night dexamethasone test. Laboratory tests performed during his hospital stay showed an increased level of serum cortisol without suppression of night dexamethasone test, increased level of ACTH, and decreased testosterone level, increased 17 OHCS in urine. CT scan of adrenal and pituitary glands, and chest x-ray were normal. The patient was discharged with an appointment made for surgical exploration of the pituitary gland. Transnasal selective partial hypophysectomy was performed, however, excisional biopsy showed no microadenoma while the symptoms persisted postoperatively. The patient received TCT hypophysis in a maximal dose, and elevated ACTH level was found to persist after 37 days of treatment. One year later, the patient was readmitted for persistent cushinoid appearance. After complete investigations for ectopic ACTH secreting tumor, chest x-ray showed an infraclavicular, circular, sharply demarcated inhomogeneous lesion of the left lung, 2x3 cm in size. Three months later, lobectomy was performed and pathohistologic examination pointed to a carcinoid (argentaffinoma). During hospitalization, the symptoms of Cushing's syndrome regressed. In conclusion, CRH test which usually distinguishes between hyperadrenocorticism associated with ectopic ACTH secretion and hypersecreting adrenal tumors is sometimes misleading because of the large overlap in normal and abnormal responses. In this case, chest or abdominal CT scan or MRI should be performed, because these are the most common sites of ectopic ACTH secreting tumors.

Key words: *ACTH syndrome - ectopic; Corticotropin - secretion; Cushing's syndrome - pathology*

Introduction

Ectopic adrenocorticotropic hormone (ACTH) secretion was the first paraneoplastic endocrine syndrome described in the literature. The most common tumors associated with ectopic ACTH production are small-cell lung cancer and atypical carcinoids. High cortisol levels have also been described in patients with adenocarcinoma and large-cell carcinoma of the lung, other carcinoid tumors, thymoma, neural crest tumors, medullary carcinoma of the thyroid, and bronchial adenomas. Most patients have hypokalemia and metabolic alkalosis. Patients rarely live long enough for frank Cushing's syndrome to develop. However, diabetes, hypertensio, nedema, muscle wasting, central obesity, moon facies, and striae may develop in those with extremely high cortisol levels. Diagnosis is confirmed by a plasma ACTH level of more than 200 pg/mL, plasma cor-

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tisol level of more than 40 mg/dL without diurnal variation, or positive dexamethasone suppression test.

Several paraneoplastic syndromes are associated with bronchogenic carcinoma. Sensitive and specific techniques have enabled identification and serial measurement of a variety of polypeptides and other physiologically active substances secreted by these tumors, especially small-cell cancers. Patients may become symptomatic from these paraneoplastic disorders before their primary tumor becomes clinically apparent. For example, the onset of Cushing's syndrome or polymyositis in individuals who are middle-aged or older should suggest the possible presence of bronchogenic cancer. To some extent, tumor-produced products (e.g., ACTH and HGH) can serve as biomarkers of tumor activity.

Case Report

C.Z., a middle-aged (born 1956) driver from Karlovac, married, two children, weight 75 kg, height 170 cm; at the age of 30, admitted to the endocrinology ward for suspicion of Cushing's syndrome. The patient had been well until a year before, when he experienced rounded (moon) face, obesity, dryness of skin, decreased libido and impotence, and echimosis after minimal trauma. Outpatient examination showed high plasma cortisol levels without suppression of night dexamethasone test on several occasions.

Laboratory tests performed during his hospital stay showed an increased level of serum cortisol (1181 nmol/L at 8 a.m. and 1319 nmol/L at 5 p.m.) without suppression of night dexamethasone test (654 nmol/L) and changed rhythm of daily cortisol secretion, increased level of ACTH (29.3 pmol/L at 8 a.m. and 45.5 pmol/L at 5 p.m.), decreased testosterone level (8.3 nmol/L), and increased 17 OHCS in urine (73.1 nmol/L) which persisted after four days of dexamethasone test (72.1 nmol/L). Skull x-ray, computed tomography (CT) scan of adrenal and pituitary glands, and chest x-ray were normal. Laboratory tests for Addison's disease, performed because of the general hyperpigmentation of the skin, were negative.

The patient was discharged with an appointment for surgical exploration of the pituitary gland, irrespective of the CT scan results, because CT scan is known to only show tumors larger than 2 mm, while those of less than 2 mm cannot be visualized by CT but are usually detected on operation.

Transnasal selective partial adenomectomy, performed in Hamburg, did not show any microadenoma. Clinically, the symptoms persisted postoperatively (serum cortisol 1380 and 1325 nmol/L at 8 a.m. and 5 p.m., respectively). The patient was referred to nuclear medicine department for postoperative radiotherapy and/or cyproheptadine for suspicion of a suprasellar tumor, because ectopic ACTH secretion was not proved, whole colonoscopy indicated polyps, another chest x-ray and CT scan of the pituitary were negative, and CT scan of the adrenal glands showed mild hyperplasia.

The patient received TCT hypophysis in a maximal dose of 8074 R and a focal dose of 4800 R with cyproheptadine (Periactin, 3 tbl twice daily); after 37 daily treatments, the ACTH level was still elevated (49.5 and 45.7

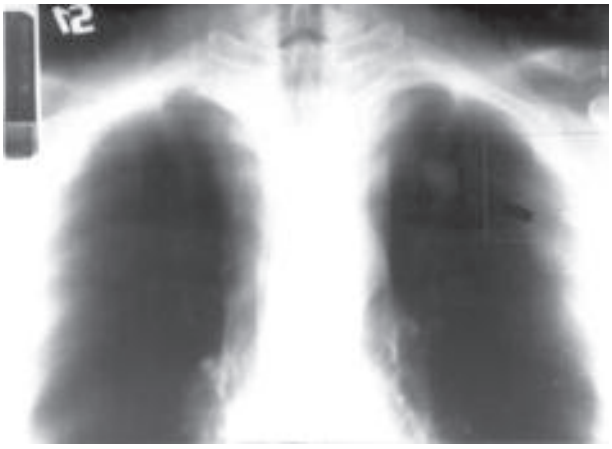

Fig. 1. Chest x-ray before operation

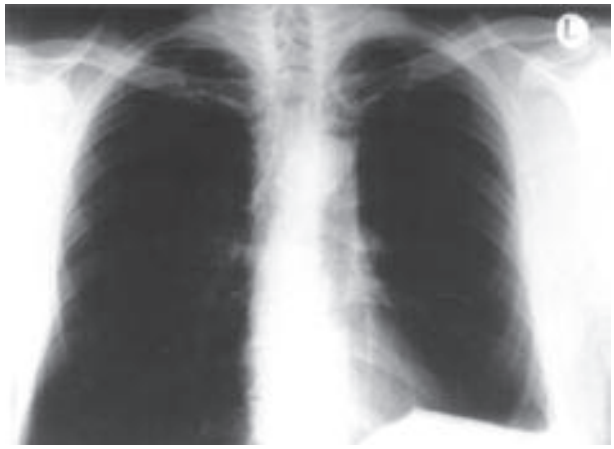

Fig. 2. Chest x-ray after operation

pmol/L at 8 a.m. and 5 p.m., respectively), and daily rhythm of plasma cortisol was normal with a limited degree of suppression after the use of dexamethasone (557 nmol/L).

One year later, the patient was readmitted for persistent cushinoid appearance, buffalo hump, and skin striae. Hormonal tests showed increased serum cortisol (958 and 839 nmol/L at 8 a.m. and 5 p.m., respectively) and ACTH (48.8 and 44.6 pmol/L at 8 a.m. and 5 p.m., respectively), which were not suppressed after 5-h infusion of dexamethasone (618 nmol/L), while 750 mg Metopirone test (serum cortisol 1005 and 483 nmol/L, and ACTH 33.3 and 66 pmol/L at 8 a.m. and 5 p.m., respectively) and CRF test failed to produce appropriate results. On repeated examination for ectopic ACTH secreting tumor, chest x-ray showed an infraclavicular, circular, sharply demarcated, inhomogeneous lesion of the left lung, 2x3 cm in size. Three months later, lobectomy was performed and pathohistologic examination pointed to a carcinoid (argentaffinoma). Fig. 1, 2.

Postoperatively, the patient developed hypocortisolism, probably due to the damage to basopilic cells by operation and radiation, and prolonged suppression of the paraendocrine secretion of ACTH from pulmonary carcinoid. X-ray of the thorax and abdomen showed no metastases. During hospital stay, the symptoms of Cushing's syndrome regressed, however, there was persistent hypokalemia (2.6 mEq/L; normal 4.1-5.0 mE1/L), which was explained as a nutritive deficiency due to the decreased serum and urine levels of aldosterone (69 pmol/L and 1 nmol/dU, respectively) and cortisol.

Methods

The level of serum cortisol was determined by the standard radioimmunoassay (RIA) method allowing exact cortisol concentration to be measured in a small serum volume. 125I labeled hormne was used. Both 125I-cortisol and unlabeled serum cortisol bind to specific antibody according to their concentration in the radioactive mixture. The amount of 125I-cortisol binding to the antibody is reversely reciprocal to the concentration of unlabeled serum cortisol.

Venous blood samples of 5 mL were obtained in the morning (8 a.m.) and afternoon (5 p.m.) after 30-min bed rest. In a healthy person, the cortisol secretion rate is higher in the morning (6-8 a.m.) and lower in the evening (4-6 p.m.), due to the cyclic hypothalamic secretion of CRF. At our laboratory, normal cortisol values are 138-800 nmol/L at 8 a.m. and 50%-70% of the morning values at 5 p.m.

In dexamethasone suppression test performed at bedtime (11 p.m.), two 0.5-mg dexamethasone tablets were administered per os. Venous blood samples were obtained at 8 a.m. and 5 p.m. on the day following the administration of dexamethasone. Normal cortisol values are less than 80 nmol/L.

Urinary cortisol excretion in 24-h collection is the most useful test. It has a better specificity than the overnight 1-mg dexamethasone suppression test and escapes various pitfalls pertaining to dexamethasone metabolism and drug interference.

Skull x-ray will often show evidence of osteopenia of the dorsum sellae, and provide the neurosurgeon with useful indications on the bone landmarks and state of pneumatization of the sphenoidal sinus.

CT scanning has for a long time been the only imaging technique for the pituitary gland. CT can achieve a sensitivity no higher than 50%. A microadenoma will appear as a hypodense round lesion; the mass effect on the pituitary stalk and diaphragm will depend on the size of the lesion. The specificity of CT is not perfect, since abnormal images are not infrequent and may provide false-positive results in patients with other causes of Cushing's syndrome.

Magnetic resonance imaging (MRI) without and with gadolinium enhancement has significantly improved the ability to detect pituitary microadenomas in Cushing's disease. Several studies have shown that many patients with a negative CT have a positive MRI finding. A hypointense signal that is better detectable upon enhancement is typical of microadenoma.

Discussion

ACTH-dependent hyperfunction of the adrenal gland cortex may occur due to hypersecretion of ACTH by the pituitary, secretion of ACTH by a non-pituitary tumor such a small-cell carcinoma of the lung (ectopic ACTH syndrome), or administration of exogenous ACTH. Patients with Cushing's disease may have a basophilic adenoma of the pituitary or a chromophobe adenoma. Microadenomas can usually be visualized by CT or preferably MRI scan, using high resolution technique enhanced by gadolinium. Some microadenomas are difficult to visualize even with these modalities. In some cases, no histologic abnormality is found in the pituitary despite clear evidence of ACTH overproduction.

Plasma cortisol is normally 5-25 mg/dL in the early morning (6-8 a.m.), and declines gradually to less than 10

mg/dL in the evening (6 p.m. and after). Patients with Cushing's syndrome usually have elevated morning cortisol levels and lack of the normal diurnal decline in cortisol production, so that evening plasma cortisol levels are above normal and total 24-h cortisol production is increased. Free urinary cortisol, the best assay for urinary excretion, is elevated in Cushing's patients and is subject to only minimal increase in obese patients (normal 20 to 10 mg/24 h). Peroral administration of 1 mg dexamethasone at 11-12 p.m. with plasma cortisol measurement at 7-8 a.m. on the next morning has been used as a screening test for Cushing's snydrome. In patients with adrenal tumors, cortisol production is independent of ACTH and therefore dexamethasone will have no suppression effect. In patients with the ectopic ACTH syndrome, the production of ACTH by a non-pituitary tumor is almost always unaffected by dexamethasone; hence, urinary steroids remain unchanged.

The CRH test usually distinguishes between hyperadrenocorticism associated with ectopic ACTH secretion and hypersecretion from adrenal tumors in which no response occurs, and the pituitary form of Cushing's disease in which the response is normal or enhanced. However, this test is sometimes misleading because of a large overlap in normal and abnormal reponses. It is most valuable when combined with a positive dexamethasone suppression test.

When the pituitary is the source of excessive ACTH secretion, the standard approach is to perform a trans-sphenoidal exploration of the pituitary and excise the tumor if one is found. If no tumor is found, some physicians proceed to hypophysectomy, but most believe that the next step is supervoltage irradiation of the pituitary, delivering 4000 to 5000 R. In special centers, heavy particle beam irradiation, providing about 10 000 R, is also often successful. Response to irradiation may require several months.

Adrenocortical neoplasms are surgically removed. Patients must receive supplementary cortisol intra- and postoperatively, since their non-tumorous adrenal cortex will be atrophic and suppressed. Where possible, the treatment for ectopic ACTH syndrome consists of removing the non-pituitary tumor producing ACTH. However, in most cases the tumor is disseminated and cannot be excised.

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Sažetak

PRIKAZ BOLESNIKA S EKTOPIČNOM SEKRECIJOM ACTH I ZNACIMA CUSHINGOVA SINDROMA

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Prvi paraneoplastični endokrini sindrom opisan u literaturi bila je ektopična sekrecija ACTH. Najčešći tumori udruženi s ektopičnom sekrecijom ACTH su mikrocelularni karcinom pluća i atipični karcinoidi. Visoke razine kortizola opisane su i u bolesnika s adenokarcinomom i karcinomom velikih stanica pluća, karcinoidima, timomom, tumorima neuralnog grebena, medularnim karcinomom štitnjače i bronhalnim adenomom. Bolesnici rijetko žive dovoljno dugo da razviju manifestan Cushingov sindrom. Opisan je slučaj 30-godišnjeg muškarca koji je primljen na odjel s kliničim znacima Cushingova sindroma. Ambulantno ispitivanje pokazalo je u više navrata visoke razine kortizola koji se nije snižavao u kratkom deksametazonskom testu. Tijekom boravka u bolnici je uz već navedeno uočena visoka razina ACTH, sniženi testosteron i povišen 17 OHCS u mokraći. CT nadbubrežnih žlijezda i Rtg snimka prsnog koša bili su uredni. Bolesnik je otpušten uz dogovor za kiruršku eksploraciju hipofize, te je učinjena transnazalna djelomična hipofizektomija. Ekscizijska biopsija nije pokazala znakove tumora, a klinički znaci Cushingova sindroma ustrajali su nakon operacije. Bolesnik je podvrgnut radioterapiji hipofize u maksimalnoj dozi, međutim, vrijednosti ACTH su još uvijek bile povišene. Nakon godinu dana bolesnik je ponovno primljen na odjel zbog ustrajnih znakova Cushingova sindroma. Nakon potpune obrade u smislu traženja ektopične sekrecije ACTH, snimka prsnoga koša pokazala je infraklavikularno oštro ograničenu, nehomogenu sjenu u plućima, veličine 2x3 cm. Tri mjeseca kasnije učinjena je lobektomija, a patohistološki nalaz je ukazao na karcinoid (argentafinom). Tijekom hospitalizacije simptomi Cushingova sindroma su se povukli. U zaključku, CRH test koji obično razlikuje hiperadrenokorticizam udružen s ektopičnom sekrecijom ACTH i hipersekreciju iz adrenalnih tumora, ponekad je neprikladan zbog značajnog preklapanja u normalnom i abnormalnom odgovoru. U tom slučaju, nužan je detaljan pregled prsnoga koša i trbuha, budući da su to najčešća sijela tumora koji ektopično izlučuju ACTH.

Ključne riječi: *Sindrom ACTH - ektopični; Kortikotropin - sekrecija; Cushingov sindrom - patologija*