Asian Jr. of Microbiol. Biotech. Env. Sc. Vol. 21, No. (4) : 2019 : 862-864

ISSN-0972-3005

PITUITARY ACTH-DEPENDENT CUSHING'S SYNDROME, A CASE REPORT

HARI HENDARTO AND FEMMY NURUL AKBAR

Department of Internal Medicine,
Faculty of Medicine, Universitas Islam Negeri, Syarif Hidayatullah, Jakarta, Indonesia

(Received 18 February, 2019; accepted 2 April, 2019)

Key words : *Pituitary adenoma Cushing's disease, Pituitary, ACTH-dependent Cushing's syndrome*

Abstract – Cushing's disease is a rare disease that is caused by the overproduction of cortisol caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. The diagnosis for Cushing's disease is made by laboratory testing, which demonstrates the supraphysiological levels of circulating cortisol. Magnetic Resonance imaging (MRI) enhances detection of ACTH-secreting pituitary adenomas. If left untreated, an ACTH-secreting pituitary adenoma often results in diminished patient survival and worsened quality of life. Early diagnosis and appropriate treatment can reverse the signs and symptoms and leads to a significantly improved quality of life. Here we present a case report of a young obese female with diagnosis of pituitary ACTH-dependent Cushing's syndrome.

INTRODUCTION

The term Cushing's disease, or pituitary ACTH-dependent Cushing's syndrome, is specifically applied to excess glucocorticoid production resulting from an ACTH hypersecretion, induced by pituitary tumors, causing over production of cortisol (Castinetti *et al.*, 2012; Pendharkar *et al*., 2015). Cortisol secretion is released from the anterior pituitary gland, which is controlled by ACTH. Cushing's disease is distinct from Cushing's syndrome; the latter refers to hypercortisolism of any etiology (Pendharkar *et al*., 2015). Cushing's disease first described by Harvey Cushing in 1932, represents the most frequent cause of Cushing's syndrome (Castinetti *et al.*, 2012; Lefkowitz *et al*., 2017). Diagnosis is often difficult and is seen mostly in women. None of the signs or symptoms are pathognomonic of the syndrome, and many signs or symptoms are found in the general population (Lefkowitz *et al*., 2017). Common chief complaints include weight gain, amenorrhea, increased facial hair, changes in the face, neck, and abdomen, with muscle wasting of the lower extremities. If left untreated, diabetes mellitus and hypertension can occur and often results in diminished patient survival and worsened quality of life, thus it is important to make an early diagnosis (Buliman *et al.*, 2016). Early diagnosis and appropriate treatment can reverse the signs and symptoms and lead to a significantly improved quality of life. The main purpose of this study is to present a case report of a youngobese female with diagnosis of pituitary ACTH-dependent Cushing's syndrome.

CASE REPORT

A 27-year-old obese female was referred to our hospital with chief complains of increased weight and wanted to take part in weight reduction program. In the last 2 years, she has noticed irregular menstrual period and she started to put on weight rapidly to almost 20 kg. She had noticed that she had a faint moustache, and also felt that her cheeks were becoming fuller and rounder. She also noted enlargement of her abdomen with purple striae appeared since a year ago. These striae later appeared on her thighs, underarms, breasts and trunk. She felt very distressed over the change in her physical appearance. She had mood changes, depression and also sleep disturbance. There was no previous medical or surgical history and no family history for endocrine disease.

During examination the woman showed typical clinical signs of Cushing's syndrome. The patient's height and body weight were 155 cm and 69 kg (BMI 28.72 kg/m^2). Physical exam showed moon face, central obesity, multiple purple striae on the abdomen. The rest of the exam was within normal functional limits. No neurological deficits were

observed, including her visual field. Cushing's disease was suspected, the patient was admitted to the endocrinology department. Studies performed during the patient's first admission showed the following results: cortisol 8 a.m. = 33.22 μg/dL (6.2–19.4 μg/dL), cortisol 11 p.m. = 23 μg/dL (1–4 μg/dL), early morning ACTH = 60 pg/mL (10–50 pg/mL). Additional testing of the other pituitary axes showed no insufficiency (Table 1).

Imaging studies was done to determine the source. If the blood ACTH level is detectable or elevated, pituitary protocol MRI is also done to see if there is a visible tumor. The founding from her MRI with contrast on her pituitary gland clearly showed a 5×4x3 mm small pituitary micro-adenoma in the right half of her pituitary gland. No overt compression of the optic chiasm was observed.

The results suggested ACTH-dependent Cushing's syndrome. The patient was then directed to a neurosurgical department and transsphenoidal resection of her pituitary microadenoma was accomplished. An ACTH-secreting pituitary adenoma was confirmed by pathologic examination. Postoperatively her serum cortisol fell to tonormal. She received dexamethasone because the sudden postoperative fall in serum cortisol can cause symptoms of dizziness, tiredness and fatigue or in worst case scenario it will put her at risk on Addisonian crisis. Six months later, she had lost 8kg. The patient's height and body weight were 155 cm and 61 kg, (BMI 25.39 kg/m^2). Her face was thinner. Patient stated she was better than before surgery. The signs and symptoms of hypercortisolism, including the psychological problems, improved gradually within several months following surgery. Patient was successfully treated with surgery and achieved remission from her Cushing's disease.

DISCUSSION

Cushing's syndrome can be caused by a tumor of the adrenal glands, the lungs, or the pituitary gland.

Table 1. Results of the Hormonal Evaluation of Pituitary Function

Result	Normal	Range
Luteinizing hormone	7.13	1.7-8.6 mIU/mL
Follicle stimulating hormone	5.65	3.5-12.5 mIU/mL
Prolactin	23.26	4.79-23.3 ng/mL
FreeT4	16.27	10.60-19.40 pmol/L
TSHs	0.21	0.2-5ìIU/mL

When the tumor produces too much ACTH, it causes over production of cortisol by the adrenal glands. If the source is the pituitary, it is called Cushing's disease. The prevalence of Cushing's disease is of 40:1.000.000 people and more often occurs in women (Buliman *et al.*, 2016). Hypercortisolism state in patients with Cushing's disease include several clinical signs: acne, hirsutism, hair loss, weight gain, lipodystrophy, round face, extra fat around the neck, skin bruising, abdominal striae, and menstrual irregularity (Zada, 2013; Shaver *et al*., 2015). Medical conditions include hypertension, diabetes mellitus, unexplained osteoporosis and arthralgia (Zada *et al*., 2013; Shaver *et al*., 2015). The incidence of psychiatric abnormalities including anxiety, depression, insomnia, poor concentration, psychosis, euphoria, short-term memory or cognitive deficits has been assessed in patients with Cushing's Disease (Zada *et al*., 2013; Shaver *et al*., 2015; Lonser*et al*., 2017).In this patient, almost all the symptoms mentioned above have been obtained. The diagnosis for Cushing's disease is made by laboratory testing, which demonstrates the consistent overproduction of cortisol. Cushing's syndrome is either ACTH-dependent (pituitary adenoma or ectopic tumor) or ACTH-independent (adrenal tumor) mechanism. Checking plasma ACTH should immediately follow the diagnosis of Cushing's syndrome.

Most cases of Cushing's syndrome are ACTH-dependent (80%) and most instances of ACTH-dependent Cushing's syndrome originate from a pituitary tumor or Cushing's disease (Prevedello *et al*., 2009). Once hypercortisolism is confirmed, low plasma ACTH value below normal,establishes ACTH-independent Cushing's syndrome, whereas high plasma ACTH, point to ACTH-dependent Cushing's syndrome. Normal level of plasma ACTH values should prompt a CRH-stimulation test for clarification of ACTH dependence (Prevedello *et al*., 2009). ACTH-dependent Cushing's syndrome can be easily explored by ACTH measurements, but the differential diagnosis between pituitary and ectopic Cushing's disease is difficult. High-dose dexamethasone suppression testing can be used to distinguish between ACTH-dependent causes of Cushing's syndrome. High doses (8 mg) of dexamethasone can suppress cortisol secretion in Cushing's disease patients while ectopic ACTH-secreting tumors typically do not respond (Lonser *et al*., 2017).

Evaluation of the Sellar region by using magnetic

resonance investigation (MRI) was critical in the diagnosis of Cushing's disease because it evaluated the preoperative anatomic structure of the pituitary gland and confirmed the presence or absence of a pituitary adenoma. In ACTH-dependent Cushing's syndrome, MRI of the Sella will find a pituitary adenoma in about 60% of cases (Prevedello *et al*., 2009). Data from large surgical series indicate that over 90% of ACTH-adenomas are microadenomas (< 1 cm in diameter) with a mean diameter of 6 mm at time of diagnosis (Lonser *et al*., 2017). If biochemical tests correlate with Cushing's disease and a significant size pituitary adenoma is visualized on the MRI, the diagnosis of Cushing's disease is established. MRI with contrast was recommended because pituitary adenomas have a homogeneous enhancement, which distinguishes them from the normal pituitary tissue (Buliman *et al*., 2016). Although MRI may confirmthe presence of a pituitary adenoma, in upto 40 % of all the cases, an adenoma remains undetectable. When a lesion is not visible or appears smaller than6 mm on imaging, bilateral inferior petrosal sinus samplingis recommended to clearly distinguish between CD and ectopic ACTH production (Ramos *et al*., 2016).

The gold-standard treatment for Cushing's disease is trans sphenoidaladenomectomy (Pendharkar *et al*., 2015). Cushing's disease treatment aims to improve clinical manifestations by the tumor mass resection with the decompression of the optic nerve and chiasm.

Thus, normalizing the hormone secretion in both the hormonal hypersecretion and insufficiency, obtaining an anatomopathological confirmation and, not least, reducing the rate of recurrence. At the same time, the preservation of the normal surrounding tissue integrity should be followed, while avoiding the possible complications (Buliman *et al*., 2016). Large tumor size, invasion into surrounding structures, and aggressive histological factors have been suggested to correlate with higher recurrence rates, whereas smaller tumor size and greater neurosurgical experience of the primary surgeon are associated with lower rates of recurrence (Pendharkar *et al*., 2015). However, a recent meta-analysis demonstrated that age, sex, tumor size, and macroscopic invasion were not reliable predictors of recurrence (Pendharkar *et al*., 2015). When treatment directed at the Sella fails, bilateral adrenalectomy is highly effective in controlling hypercortisolism (Prevedello *et al*., 2009).

After surgery, the patient was carefully monitored, measuring cortisol levels. Her cortisol level would be checked to see if her pituitary was "waking up" and stimulating normal cortisol product. During this time, patients receive glucocorticoid replacement (dexamethasone). Typically, the suppressed normal pituitary gland corticotropes in the hypothalamic-pituitary-adrenal axis typically recovers slowly over the next 6 to 12 months until normal cortisol levels are achieved and steroid replacement can be discontinued (Prevedello *et al*., 2009; Hsu *et al*., 2010; Lonser *et al*., 2017).

CONCLUSION

Cushing disease is a complicated medical problem. The surgical treatment could be curative when a tumor is confirmed.

REFERENCES

Buliman, A., Tataranu, L.G., Mirica, A. and Dumitrache, C. 2016. Cushing's disease: a multidisciplinary overview of the clinical features, diagnosis and treatment. *J Med Life.* 9 (1) : 12-18.

Castinetti, F., Morange, I., Conte-Devolx, B. and Brue, T. 2012. Cushing's disease. *Orphanet J Rare Dis.* 7(1): 41.

Cuevas-Ramos, D., Lim, D.S. and Fleseriu, M. 2016. Update on medical treatment for Cushing's disease. *Clin Diabetes Endocrinol*. 2 : 16.

Hsu, P.Y., Tung, Y.C., Lee, C.T., Lo, F.S., Wu, M.Z., Tsai, W.Y. and Tu, Y.K. 2010. Cushing's disease in children: Report of Three Cases. *Pediatr Neonatol*. 51 (5) : 303–307.

Lefkowitz, E.G., Cossman, J.P. and Fournier, J.B. 2017. A case report of Cushing's disease. presenting as hair loss. *Case Rep Dermatol.* 9 : 45–50.

Lonser, R.R., Nieman, L. and Oldfield, E.H. 2017. Cushing's disease: pathobiology, diagnosis, and management. *J Neurosurg*. 126 : 404–417.

Pendharkar, A.V., Sussman, E.S., Ho, A.L., Hayden Gephart, M.G. and Katznelson, L. 2015. Cushing's disease: predicting long-term remission after surgical treatment. *Neurosurg Focus*. 38 (2) : E13.

Prevedello, D., Challinor, C., Nestor, D., Tomycz, N., Gardner, P., Carrau, L., Snyderman, C. and Kassam, A.B. 2009. Diagnosing, managing Cushing's disease: a multidisciplinary overview. *Review of Endocrinology*. 19-24.

Shaver, D. 2015. Case report: patient presenting with Cushing's disease. *Surg Neurol Int*. 6 (Suppl 6): S268-2670.

Zada, G. 2013. Diagnosis and multimodality management of Cushing's disease: a practical review. *Int J Endocrinol* . 893781.