Exogenous Cushing's Syndrome with Subsequent Secondary Adrenal Insufficiency in Patients with Long Term Steroid Usage

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Abstract

Exogenous Cushing's syndrome is a collection of symptoms and clinical signs due to elevated levels of glucocorticoids (cortisol) in the blood because of prolonged consumption of glucocorticoid drugs. Glucocorticoids were introduced in the 1950s and have been used for anti-inflammatory treatment. Withdrawal of glucocorticoids can lead to complications of secondary adrenal insufficiency caused by suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Male, 28 years old, with weakness in both hands and feet throughout 3 days before admission to hospital. Other complaints include nausea (+), vomiting (+), diarrhea (-). He had been taking dexamethasone daily in the past 3 years until one month ago when he suddenly stopped. Physical examination revealed moon facies (+), striae (+) in the abdomen, and motor strength of 2 in all four extremities. Laboratory: K 2.0 mmol/L, Mg 0.8 mg/dL, GDA 64 mg/dL, Total cholesterol 240 mg/dL, cortisol 18.67 ng/mL, ACTH 2.1 pg/mL. The patient was diagnosed with exogenous Cushing's syndrome based on a history of long-term use of dexamethasone. Physical examination revealed moon face, buffalo hump, purplish striae, and hypertension. The patient stopped dexamethasone consumption suddenly and is consequently experiencing secondary adrenal insufficiency at the present time. As evidenced by laboratory values, there was a decrease in serum cortisol (18.67 ng/mL), as well as a decrease in serum ACTH (2.1 pg/mL). Based on the history of dexamethasone use, physical examination, and laboratory results, this patient had exogenous Cushing's syndrome. Sudden discontinuation of dexamethasone results in withdrawal symptoms in the form of secondary adrenal insufficiency as indicated by low cortisol and ACTH values.

Keywords: *Cushing's syndrome, glucocorticoid, withdrawal, adrenal insufficiency.*

Introduction

Cushing's syndrome is a term used to describe conditions resulting from increased concentrations of glucocorticoids (cortisol) in the blood circulation. The incidence of Cushing's syndrome is 0.7–2.4:1,000,000 population per year. This condition can be caused by factors outside (exogenous) or inside the body (endogenous)[1]. Corticosteroid use is the most common cause of Cushing's syndrome, the exogenous type of which depends on the dose and potency of the steroid used and the duration of usage[1–3].

Glucocorticoids were introduced in the 1950s, and have been used for anti-inflammatory, autoimmune and neoplastic treatment. Cushing's syndrome can manifest as a result of Glucocorticoids usage for treatment over a long period of time. Withdrawal of corticosteroids without tapering off can cause withdrawal symptoms, namely secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis[3,4].

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Adrenal insufficiency is a pathological condition characterized by decreased glucocorticoid production. Adrenal insufficiency is rare, with an incidence rate of <0.01% in the general population. It can be classified as primary and secondary, with the latter occurring when exogenous steroids suppress the hypothalamic-pituitary-adrenal (HPA) axis, resulting in insufficient stimulation of the adrenal glands to secrete adrenocorticotropic hormone (ACTH)[5,6].

Case Report: A man aged 28 years came with complaints of weakness in both hands and feet for 3 days prior to hospital admission. Other complaints include fever (+), nausea (+), vomiting (+), and decreased appetite. Bowel movement and bladder within normal limits. The patient was diagnosed with gout (3 years ago) and had since been routinely taking dexamethasone. In a day, the patient could take 9 to 15 tablets of dexamethasone until one month ago when the patient suddenly stopped.

Physical Examination 26 August 2020 (Upon arrival at the ER): The patient was generally weak; conscious (Compos mentis) with GCS 4-5-6; had blood pressure of 132/80 mmHg, pulse of 96×/minute, breathing of 22×/minute, and axillary temperature of 36.5 ℃. Other physical examinations revealed moon face (+), buffalo hump (+), and purplish (+) striae on the abdomen. The acral extremities felt warm, and there was atrophy of the lower limb muscles, as well as oedema of both legs. Neurological examination revealed paraparesis with motor muscle strength of 2 for all extremities.

Supporting Examination:

Table 1. Hematological Examination.

Parameter	26-08	27-08	28-08	31-08	02-09	Normal range
Hb (g/dL)	9.0	9.6	8.8	9.6	9.7	13.3-16.6
RBC (10^6/uL)	3.36	3.66	3.33	3.81	3.65	3.69-5.46
HCT (%)	26.4	38.3	27.4	30.4	29.4	41.3-52.1
MCV (fL)	84.7	81.5	82.3	79.8	80.5	86.7-102.3
MCH (pg)	26.6	26.2	26.4	25.2	26.6	27.1-32.4
MCHC (g/dL)	34.1	33.9	32.1	31.6	33.0	29.7-33.1
WBC (10^3/uL)	11.22	9.84	9.68	12.73	13.5	4.1-11.0
Eo (%)	1.9	2.1	2.2	2.5	1.5	0.6-5.4
Baso (%)	0.4	0.8	0.8	0.7	0.4	0.3-1.4
Neut (%)	82	70.3	59.3	69.1	86.6	39.8-70.5
Lymph (%)	14.8	17.6	27.3	19.2	8.4	23.1-49.9
Mono (%)	10.5	9.2	10.4	8.5	4.6	4.3-10
PLT (10^3/uL)	599	367	548	585	553	150-450
RDW (%)	12	13.5	14.0	13.2	14.5	12.2-14.8
LED (mm/jam)					52	
PPT (second)	11.6	13.7				9-12
APTT pend.(detik)	27.9	30.0				23-33

Table 2. Clinical Chemistry Examination and Urinalysis.

Parameter	26-08	28-08	31-08	1-09	2-09	4-09	Normal range
Na (mmol/L)	137	137	137	138	136	143	136-145
K (mmol/L)	2.3	3.4	3.4	2.9	3.4	3.1	3.5-5.1
Cl (mmol/L)	98	98	104	100	99	103	98-107

Parameter	26-08	28-08	31-08	1-09	2-09	4-09	Normal range
Ca (mg/dL)				6.8			8.5-10.1
Mg (mg/dL)	0.8	1.2	1.4		1.3	1.4	1.8-2.4
BUN (mg/dL)	4	2	9				7-18
SC (mg/dL)	1.2	1.2	0.9				0.6-1.3
Alb (g/dL)	2.61	2.8	2.9		3.0		3.4-5
GDA (mg/dL)	67	90			109		<200
SGOT (U/L)	56	59					L: 0-50, P: 0-35
SGPT (U/L)	39	47					L: 0-50, P: 0-35
Chol (mg/dL)						240	0-200
HDL (mg/dL)						44	40-60
LDL (mg/dL)						164	0-90
TG (mg/dL)						160	30-150
CRP (mg/dL)	13	14.67					0-1
Cortisol (ng/mL)		18.67				19.58 (Dexamethasone Suppression Test)	Morning serum (08.00-10.00): 57.2-194.2 Afternoon serum (16.00-18.00): 20.2 -131.0
ACTH (pg/mL)					2.1		7.4 – 64.3
Urinalysis	26-08	28-08	31-08	1-09	2-08	4-08	Normal range
pH		7.5					
Urine Kalium		27.75					35-80
Urine Natrium		122.5					30-300
Urine Chloride		145					85-170

Table 3. Blood Gas Analysis.

Blood Gas Analysis	26-08	28-08	Normal range
pH	7.53	7.58	7.35-7.45
pCO_2	46	37	35-45
pO_2	76	81	80-100
HCO_3	36.4	34.7	22-26
TCO_2	39.8	24.5	23-30
BEecf	15.7	12.8	-3.5-2
SO_2	97%	98%	94-98
$AaDO_2$	16	3	15-50
$\%FiO_2$	21	21	
Temp	37	37	

Conclusion: The results of blood gas analysis on 26-08-2020 showed a metabolic alkalosis with compensation for respiratory acidosis. Blood gas analysis tests on 28-08-2020 revealed an uncompensated metabolic alkalosis.

Table 4. Immunological Examination.

Parameter	28-08	30-08	31-08	Normal range
C3	42.7			50-12
C4	24.0			17.4-52.2
ANA Test	10.82			Neg <40, Pos >= 40
FT4		1.52	1.63	0,89-1.76
TSH		1.993	1.863	>18 y.o.: 0.55 – 4.78

Conclusion: Immunological and thyroid function examination results in the patient were within normal range.

Figure 1. Moon face (left) and purplish striae on the abdomen (right).

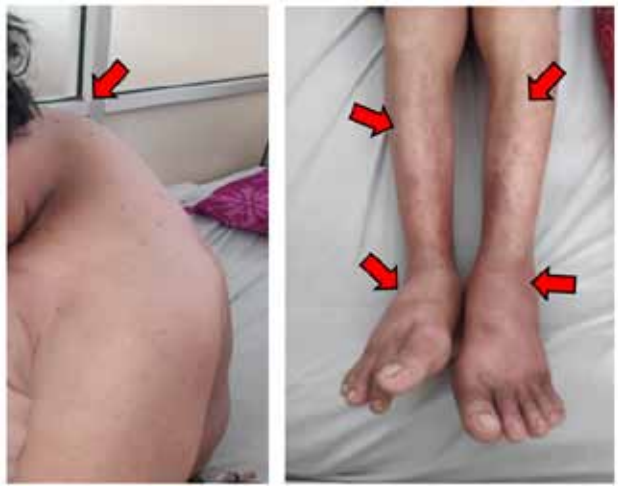

Figure 2. Buffalo hump (left) and atrophy of the lower limbs with edema in the instep (right).

Discussion

The adrenal glands, made up of the cortex and medulla, are located atop the kidneys. The adrenal gland cortex has 3 successive layers from the outside, namely the zona glomerulosa, the zona fasciculata and the reticular zone. These three layers secrete steroid hormones, namely mineralocorticoids produced by the zona glomerulosa, and glucocorticoids and androgens secreted by the zona fasciculata and the zona reticularis. Cortisol is the main product of glucocorticoids, which plays a role in regulating the metabolism of carbohydrates, proteins, and fats[7,8].

Cortisol secretion is controlled by corticotropin or adrenocorticotropic hormone (ACTH), which is secreted by the anterior pituitary, further regulated by hypothalamic hormones to secrete corticotropin (CRH). Both ACTH and CRH are controlled by cortisol via a feedback mechanism[2,7].

Glucocorticoids work as catabolic hormones, causing the breakdown of protein and fat and inhibiting protein synthesis in muscle, connective tissue, fat tissue, and lymphoid cells. This hormone also has an anabolic effect on metabolism in the liver[2,7,8].

This patient presented with complaints of weakness and fatigue. On examination, purplish striae in the armpits and lower abdomen was found. The breakdown of protein causes muscles to weaken, bone structure to thin, and lessens the skin's resistance. Stretch of the skin over the site of new fat deposition added with loss of elasticity due to protein catabolism results in rupture of blood vessels' surface. Blood seeps through the gaps caused by collagen catabolism so that purple striae can be observed[7].

The patient has hyperlipidemia characterized by increased levels of total cholesterol 240g/dL, triglycerides 160 g/dL, high-density-lipoprotein (HDL)-

cholesterol: 44 mg/dL, and low-density-lipoprotein (LDL)-cholesterol: 164 mg/dL. Hyperlipidemia occurs due to cortisol's potentiating effect on other hormones such as somatotropins and catecholamines in the lipolysis process in fat tissue[3,6,8].

Hypercortisolism causes accumulation of fatty tissue in particular places such as the face (moon face), the interscapular area (buffalo hump) and the mesenteric base (body obesity). The cause of this characteristic distribution of fatty tissue is unknown, but it is thought to be related to insulin resistance and/or elevated insulin levels[3,7]. As the case showed, this patient had moon face, buffalo hump and body obesity.

Additionally, he has hypertension, which, in patients with Cushing's syndrome, occurs due to increased production of angiotensin II as a result of increased hepatic production of angiotensinogen, increased activity of blood vessels against vasoconstrictive hormones, decreased reuptake of catecholamine degradation products, or inhibition of vasodilators such as kinins and prostaglandins[9].

Sudden discontinuation of corticosteroid use without tapering off can cause withdrawal symptoms such as secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis[5,10]. Steroid withdrawal syndrome is a syndrome with symptoms of lethargy, malaise, anorexia, myalgia, headaches, fever, and skin desquamation. Sufferers have symptoms of weakness, fatigue, anorexia, nausea, and vomiting, all of which are present in the patient.

The diagnosis of exogenous Cushing's syndrome begins with clinical suspicion based on a physical examination. Exogenous Cushing's syndrome is indicated by low serum cortisol levels in the morning. ACTH levels are also relatively low since ACTH production by the pituitary is suppressed by exogenous steroids[3].

Secondary adrenal insufficiency caused by ACTH deficiency is commonly caused by exogenous glucocorticoid therapy[3,5]. This patient had a history of long-term dexamethasone use in high doses. Taking dexamethasone will result in high levels of cortisol in the blood which in turn will reduce the secretion of ACTH.

Diagnosis of adrenal insufficiency is based on the suspicion of the patient's symptoms, clinical chemistry examination, and serum ACTH and serum cortisol levels[11]. In secondary adrenal insufficiency, ACTH suppression has minimal effect on aldosterone secretion by the zona glomerulosa, therefore, there is no manifestation of mineralocorticoid deficiency. Hyponatremia and hyperkalemia rarely occur due to the reasons above[4,5]. The patient experienced low intake and vomiting which causes low potassium and magnesium levels, resulting in complaints of weakness in the 4 extremities. The weakness ameliorated after therapy and gradually improved as the patient's potassium and magnesium levels improved.

The next step after clinical suspicion of Cushing's syndrome is to prove that there is excess secretion of the hormone cortisol and impaired feedback mechanism of the hypothalamic-pituitary-adrenal axis. For initial laboratory testing, many guidelines recommend one of the following tests: two 24-hour urine-free cortisol checks, late night salivary cortisol, 1 mg overnight dexamethasone suppression test or a longer dose dexamethasone suppression test. These three tests are the most common types of initial tests to evaluate the possibility of Cushing's syndrome. They are often faced with difficulty or entirely not available in developing countries, so, pragmatically, only morning cortisol levels are checked. For morning serum cortisol, the results are quite acceptable if the results are extremely high.

Patient's history and physical examination strongly supported the diagnosis of Cushing's syndrome, but the laboratory examination did not show an increase in serum cortisol levels. The patient had a decreased level of cortisol (serum 08.00 am), namely 18.67 ng/mL. Morning serum cortisol levels indicate adrenal insufficiency caused by corticosteroid therapy when levels are below <3μg/dL (<30 ng/mL) and indicate normal adrenal function when values are >20μg/dL (>200 ng/mL)[3,4].

Serum ACTH levels are used to differentiate primary and secondary adrenal insufficiency. Ideally, an ACTH stimulation test using synthetic ACTH (Cortrosina®, Synacthen®) is carried out by first determining the baseline serum cortisol level, then injecting 250 mcg of ACTH intravenously, followed by assessing the serum cortisol level 30 and 60 minutes after ACTH administration. Normally, after an ACTH stimulation test there will be an increase in serum cortisol levels >20 mcg/dL or an increase of >10 mcg/dL from the patient's initial cortisol level (baseline). In secondary adrenal insufficiency, there is no increase in serum cortisol

levels after the ACTH stimulation test[4,6]. The limitation in this case was that the ACTH stimulation test was not performed because no synthetic ACTH was available in the Pharmacy Unit of Dr. Soetomo Hospital Surabaya.

In the presence of secondary adrenal insufficiency, serum ACTH levels are low (<5 pg/mL [1.10 pmol/L]). The patient had a decreased serum ACTH level, namely 2.1 pg/mL[12]. This supported the diagnosis of secondary adrenal insufficiency.

Conclusion

The patient was diagnosed with exogenous Cushing's syndrome based on a history of long-term use of dexamethasone. Physical examination revealed moon face, buffalo hump, purplish striae, and hypertension. Sudden discontinuation of dexamethasone causes withdrawal symptoms, one of which being secondary adrenal insufficiency as evidenced by low morning serum values for cortisol and ACTH parameters.

Conflict of Interest: The author declare that they have no conflict of interest.

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