International Journal of Psychology and Health Science (IJPHS)
+62 813 8765 4578 http://greenpub.org editor@greenpub.org Jl. Kapt. A. Hasan, Telanaipura Jambi - Indonesia.
DOI: https://doi.org/10.38035/ijphs.v2i3
Received: June 20th, 2024, **Revised:** July 07th, 2024, **Publish:** July 20th, 2024

Overused Dexamethasone Induced Exogenous Cushing's Syndrome, Diabetes Mellitus, and Pneumonia

Putu Gede Indra Dananjaya[1], Ni Made Putri Purnama Dewi[2]
[1] Regional General Hospital Klungkung, Indonesia, Email: indra.dananjaya@gmail.com
[2] Internal Medicine Medical Staff of Klungkung Regional General Hospital, Email: putri.purnama@gmail.com

Corresponding Author: indra.dananjaya@gmail.com[1]

Abstract: Cushing's syndrome is a collection of clinical symptoms resulting from excessive exposure to glucocorticoid hormones. The cause of Cushing's syndrome can be endogenous or exogenous factors. Exogenous factors caused by long-term use of corticosteroid drugs. Clinical manifestations that can be found include weight gain, often accompanied by a moon face, central obesity, fat deposits in the dorsocervical and supraclavicular areas, proximal muscle weakness, fatigue, leg edema, easy bruising, thinning skin, and striae. We report the case of a patient with exogenous Cushing's syndrome, diabetes mellitus, and pneumonia induced by excessive dexamethasone consumption accompanied by melena. Treatment should be carried out comprehensively by paying attention to the underlying disease. Discontinuation of glucocorticoids is the main treatment and needs to be done gradually. In this case, a stress dose of glucocorticoid was not given because he was experiencing gastrointestinal bleeding.

Keyword: Cushing's Syndrome, Diabetes Mellitus, Pneumonia, Dexamethasone, Melena.

INTRODUCTION

Glucocorticoids are important pharmacological agents, especially for treating inflammation and also work with the immune system to treat a wide range of medical conditions. The widespread use of corticosteroids ranges from arthritis, allergies, respiratory tract disorders such as asthma, autoimmune diseases, to skin diseases (Geetha, K, et al, 2024). The more glucocorticoids are used for various diseases or used excessively and inappropriately, the more detrimental side effects they can cause. One of the side effects resulting from long-term use of glucocorticoids is Cushing's syndrome.

Cushing's syndrome is a collection of clinical symptoms resulting from chronic excessive exposure to glucocorticoid hormones in the blood. The main cause of Cushing's syndrome is endogenous or exogenous factors. Endogenous factors are caused by excessive production and secretion of cortisol from the adrenal glands and can be Adrenocorticotrophoic Hormone (ACTH)-dependent or ACTH-independent. Pituitary tumors associated with excessive pituitary ACTH secretion or puitary adenomas are called Cushing's disease and also

ectopic secretion of ACTH by neoplasms is the cause of ACTH-dependent Cushing's syndrome. Meanwhile, hyperplasia, adenoma and adrenal carcinoma cause ACTH-independent Cushing's syndrome. Exogenous factors are caused by long-term use of corticosteroid drugs, causing iatrogenic Cushing's syndrome (Ahmed, S. *et al*. 2021; Ratna, S. *et al*. 2022).

Excessive exposure to glucocorticoids from either endogenous or exogenous sources causes Cushing's syndrome. It is estimated to affect approximately ten to fifteen people per million residents each year in the United States, therefore it is classified as a rare disease by the Office of Rare Disease of the National Institute of Health (NIH). However, there is little epidemiological data on its prevalence and incidence. According to studies conducted in various European countries such as Italy, Spain and Denmark, the annual incidence of Cushing's syndrome ranges between 0.7 and 2.4 per million population. Cushing's syndrome is found more commonly in individuals at high risk, such as those with diabetes mellitus (especially with poor control), hypertension, and early-onset osteoporosis (especially with fractures) (Sharma, *et al.* 2015).

The diagnosis of Cushing's syndrome can be made through several steps, namely recognizing Cushing's syndrome and looking for the cause, to find out excessive cortisol, biochemical tests can be confirmed, and determining the appropriate management strategy. A detailed history is needed to distinguish exogenous or endogenous causes of Cushing's syndrome. Clinical manifestations that can be found include weight gain, often accompanied by a moon face, central obesity, fat deposits in the dorsocervical and supraclavicular areas, proximal muscle weakness, fatigue, leg edema, easy bruising, thinning skin, and striae rubrae, namely purplish pink lines on the skin. abdominal area (typical symptoms/signs of Cushing's syndrome). Apart from that, systemic disorders can also occur such as hypertension, glucose intolerance, decreased bone density and menstrual disorders in women. 3,4 The next step is to confirm with a laboratory examination. The recommended initial examination is 24-hour urinary free cortisol (24-h Urinary Free Cortisol), late night salivary cortisol, 1-mg overnight dexamethasone suppression test (DST). In developing countries, this test is usually not available, so morning serum cortisol can be checked (Tarigan, T.J.E, 2014; Dhruv Zaveri, Miral Thakkar, Pankti Solanki, Riki Patel, Jay Rane, 2022)

We report a case of exogenous Cushing's syndrome due to excessive and long-lasting consumption of the corticosteroid dexamethasone, accompanied by steroid-induced diabetes mellitus, pneumonia and anemia.

METHOD

A 54 year old woman came to the ER at Klungkung Regional Hospital with the main complaint of pain throughout the body. The patient felt pain all over the body for approximately 2 years, coming and going and getting worse so the patient had been on bed rest for 2 weeks before entering the hospital. Pain, especially in the patient's knees and feet. also complained of a dry cough without phlegm accompanied by complaints of shortness of breath for 4 days. The patient especially feels shortness of breath when the patient is active. There was swelling in both of the patient's legs and currently swelling throughout the patient's body. According to the family, the patient experienced rapid weight gain since 2 years ago. It was said that previously the patient's weight was 40 kg and currently it is around 90 kg. The patient also complained of black stools since 5 days before going to the hospital, complained of nausea but did not vomit, and had no complaints of bleeding from other places.

The patient has a history of taking the drug Dexamethasone 0.5 mg three times a day for almost 3 years, consumed regularly and purchased on the patient's own initiative without consulting a doctor. Consuming Dexamethasone is said to relieve the patient's complaints of

pain in the legs and body. If you don't take Dexamethasone, it is said that it will not improve. Apart from Dexamethasone, the patient denied taking other drugs such as anti-pain drugs.

On examination of vital signs, blood pressure was found to be 100/60 mmHg, pulse 107 times/men, respiration 20 times/minute, axillary temperature 37.8oC, oxygen saturation 98% room air. General examination revealed several signs that point to Cushing's syndrome, namely a moon face appearance and abdominal striae (Figure 1). On examination the conjunctiva appeared anemic, lung examination revealed coarse crackles in the middle lobe of the right hemithorax, bilateral edema in both lower legs. Peripheral blood investigations showed hemoglobin 5.8 g/dL with Mean Cell Volume 95 fl, leukocytes 12,380 µ/L with neutrophils dominant 85%, platelets 268,000 µ/L. On chemical examination, the results showed urea 26 mg/dL, serum creatinine 0.3 mg/dL, potassium 3.6 mmol/L, random blood glucose 219 mg/dL with HbA1c 10.3%, and albumin 2.7 g/dL. The patient had a morning serum cortisol examination during control with results of 0.1 ug/dl (3.7 – 19.4 ug/dl). On the seventh day of treatment, the patient underwent a blood culture examination and no bacterial growth was found in the blood culture. This is possibly because the patient had received antibiotic therapy before taking the blood culture. When checking fasting blood sugar, the results were 224 mg/dL (74-106 mg/dL) and blood sugar 2 hours post-prandial was 269 mg/dL (<140 mg/dL).

Based on the history, physical and supporting examination, the patient's working diagnosis was exogenous Cushing's syndrome, community-acquired pneumonia, normochronous normocytic anemia et causa acute bleeding (5.8 g/dL), steroid induced diabetes mellitus, and hypoalbuminemia (2.7 g/dL). The initial treatment for this patient was by administering Packed Red Cells (PRC) transfusions 2 bags per day with a plan of 4 bags, administering the antibiotic ceftriaxone 1 gram every 12 hours intravenously to treat pneumonia, then giving esomeprazole 80 mg (2 vials) drip in 50 cc NaCl 0.9% at a rate of 5cc/hour, and to treat pain the patient is given paracetamol 1000 mg intravenously if necessary. The patient was given Glargine insulin therapy at a dose of 8 units subcutaneously every 24 hours for the management of diabetes mellitus.

RESULT AND DISCUSSION

Cushing's syndrome is an endocrine disorder caused by high levels of glucocorticoids in the blood caused either endogenously or exogenously. Endogenous factors are caused by excessive production and secretion of cortisol from the adrenal glands and can be Adrenocorticotrophoic Hormone (ACTH)-dependent or ACTH-independent. In the ACTH-dependent group it is caused by Cushing's disease or puitary adenoma which causes excessive pituitary ACTH secretion. Ectopic Cushing's syndrome is also ACTH-dependent which is predominantly caused by tumors or neoplasms of the lung, mediastinum, pancreas, and thyroid through ACTH secretion. In ACTH-independent cases it is caused by hyperplasia, adenoma or adrenal carcinoma. The exogenous causative factor, namely and most often the cause of Cushing's syndrome, is excessive use of exogenous glucocorticoids via all routes of administration (Dhruv Zaveri, Miral Thakkar, Pankti Solanki, Riki Patel, Jay Rane, 2022; Reincke, M. dan Fleserlu, M, 2023).

The clinical manifestations are those that are often found, namely truncal obesity which often precedes other signs, weight gain, moon face, central obesity with the accumulation of fat on the face and supraclavicular area, cervical fat pad, proximal muscle weakness, fatigue easily, leg edema, easy bruising, thinning skin, osteoporosis, fractures, neuropsychiatric disorders such as depression, sleep disorders, and cognitive disorders, striae rubrae, namely purplish pink lines on the abdominal area. Some literature mentions the typical symptoms of Cushing's syndrome, namely reddish striae, plethora, easy bruising (Chaudhry HS, Singh G., 2024). The clinical symptoms of exogenous Cushing's syndrome and Cushing's disease have similar symptoms and clinical appearance. Because the symptoms and clinical appearance of the two diseases are similar, it is important to emphasize the history of glucocorticoid consumption. Apart from the history of glucocorticoid consumption, the type of glucocorticoid, duration of use and daily dose consumed need to be explored to establish a diagnosis of exogenous Cushing's syndrome. In this case, the patient presented with clinical manifestations of central obesity, moon face, weight gain, accompanied by reddish striae on the abdominal area (Figure 1). The patient's history of taking dexamethasone 0.5 mg three times a day for almost 3 years to reduce pain in the joints.

Systemically, the effects of glucocorticoids have been widely discussed in various literature. One of the systemic effects caused by glucocorticoids is the suppression of the inflammatory response. Suppression of this inflammatory response through genomic and non-genomic mechanisms which causes extracellular signal intervention via MAP kinase in macrophages, resulting in a decrease in the inflammatory response. Glucocorticoids also cause a decrease in the differentiation process of dendritic cells and apoptosis of lymphocyte and basophil cells (Soelistijo, S.A, et al, 2020) One of the risks that can occur due to decreased body immunity is pneumonia. The choice of antibiotic therapy for pneumonia patients with non-ICU hospitalization in patients with both cardiopulmonary disease and without cardiopulmonary disease, the choice of antibiotics given is fluoroquinolones, beta lactams (ceftriaxone, cefotaxime, and ampicillin) (Alwi, I, A. et al., 2019). Based on the history, physical examination and supporting In this case, the patient experienced community-acquired pneumonia (figure 2) due to decreased body immunity, where exogenous glucocorticoids induced this condition. Next, initial antibiotic therapy is given, namely ceftriaxone, which is a beta lactam.

Excessive glucocorticoid effects induce excessive glucose production, especially in the liver and skeletal muscles. In the liver, glucose production increases through direct and indirect mechanisms. The mechanism is directly through the mechanism of inducing essential enzymes for gluconeogenesis, stimulating lipolysis and proteolysis thereby increasing the substrate for gluconeogenesis, activating glucagon resulting in an increase in glucose. Indirectly, through suppression of insulin sensitivity, causing a decrease in the synthesis of glycogen stores in the liver. In skeletal muscle, glucocorticoids cause interference with insulin receptors, causing decreased glucose uptake in the blood and also decreased glycogen synthesis (Pivonello, et al, 2010). Management of diabetes mellitus in this case is given insulin Glargine 8 units every 24 hours. Patients with HbA1c >9% at the time of examination can be given insulin therapy or insulin combined with other hypoglycemic drugs (Soelistijo, S.A., et al. 2021).

In patients with exogenous Cushing's syndrome, there is still debate regarding the required dose of stress glucocorticoids. There are no agreed recommendations based on research. Glucocorticoid supplementation is given to patients who experience HPA axis suppression where moderate or severe stress occurs (in conditions of sepsis, major burns, childbirth, fractures and wounds), as well as before surgical procedures, requiring supplementation. Several studies and consensus state that the required stress dose of glucocorticoids is hydrocortisone 100 mg intravenously every 6 hours. 9 The use of corticosteroids and NSAIDs increases the risk of gastrointestinal bleeding. Several studies have shown an increase in the relative risk of gastrointestinal bleeding in patients given high doses of glucocorticoids. In this case, a stress dose of glucocorticoid was not given because the patient was experiencing gastrointestinal bleeding (Soelistijo, S.A., et al. 2021).

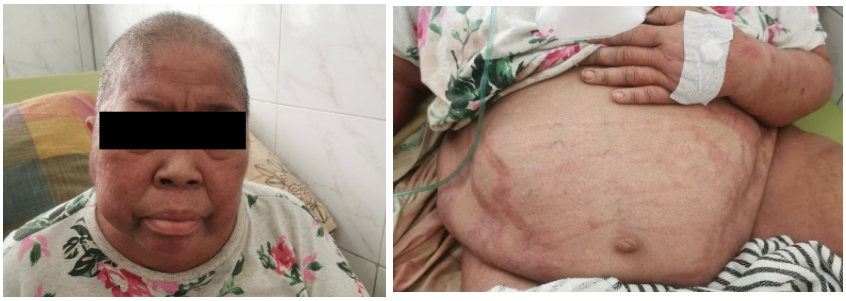

Figure 1. Clinical manifestation with moon face and abdominal striae

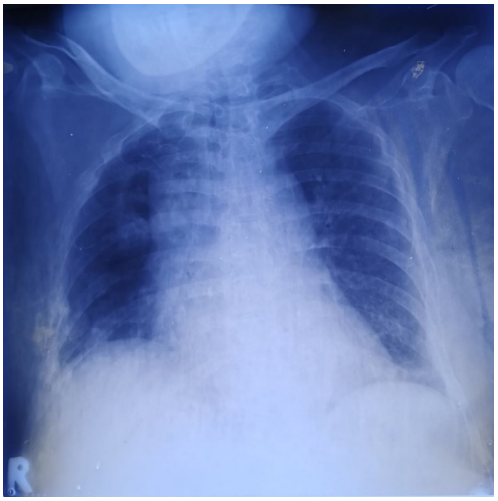

Figure 2. Thorax x-ray with pneumonia

CONCLUSION

The wider the use of a drug, the higher the risk of side effects that can occur. Exogenous Cushing's syndrome is one of the most frequently encountered Cushing's syndromes. The cause of exogenous Cushing's syndrome is prolonged exposure to glucocorticoids ranging from topical to systemic administration. Even though exogenous and endogenous Cushing's syndrome have different clinical manifestations, there are differences in how to treat these cases. Discontinuation of glucocorticoids is an important step that must be taken. During the process of discontinuing glucocorticoids, it is necessary to review the patient's condition because it is possible for a recurrence of the patient's underlying disease to occur.

REFERENCES

Ahmed, S. et al. 2021. "Topical Corticosteroid-induced Iatrogenic Cushing Syndrome in an Infant: A Case Report With Literature View." https://doi.org/10.1016/j.amsu.2021.102978

Alwi, I, A. et al. 2019. Penatalaksanaan di Bidang Ilmu Penyakit Dalam Panduan Praktik Klinis. Jakarta: PIP Interna.

Chaudhry HS, Singh G. Cushing Syndrome. 2024. Cushing Syndrome : StatPearls. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470218

Dhruv Zaveri, Miral Thakkar, Pankti Solanki, Riki Patel, Jay Rane. (2022). Dexamethasone Induced Cushing's syndrome: A Case Report, Glob Acad J Pharm Drug Res; Vol-4, Iss-3 pp- 73-75.

Geetha, K. et al. 2024. Prednisolone-Induced Cushing's Syndrome : A Case Report. World Journal of Advanced Research and Review. 21(01), 2471-2473. https://doi.org/10.30574/wjarr.2024.21.1.0056

Pivonello, et al. 2010. Pathophysiology of Diabetes Mellitus in Cushing's Syndrome. Neuroendocrinology Vol. 92(suppl 1), hal 77-81. DOI: 10.1159/000314319

Ratna, S. et al. 2022. Steroid Induced Cushing's Syndrome in an Asthmatic Patient: A Case Report. Modern Medicine Journal. https://doi.org/10.31689/rmm.2023.30.3.247

Reincke, M. dan Fleserlu, M. 2023. Cushing Syndrome A Review. Clinical Review & Education. American Medical Association. JAMA. 2023;330(2):170-181. doi:10.1001/jama.2023.11305

Sharma, et al. 2015. Cushing's Syndrome: Epidemiology and Developments In Disease Management. Dovepress. Hal 281-293. https://doi.org/10.2147/CLEP.S44336

Soelistijo, S.A, et al. 2020. Sindroma Cushing Eksogen: "Kapan Penggunaan Dosis Stres Glukokortikoid Bermanfaat?". Jurnal Penyakit Dalam Indonesia. Vol. , No. 3. Hal 181-185.

Soelistijo, S.A., et al. 2021. Pedoman Pengelolaan dan Pencegahan Diabetes Mellitus Tipe 2 Dewasa di Indonesia. PB PERKENI

Tarigan, T.J.E. 2014. Buku Ajar Ilmu Penyakit Dalam Jilid II Edisi VI: Sindrom Cushing dan Penyakit Cushing. Jakarta: Interna Publishing. Hal: 2478-2483