ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Gabriela-Mintegui/256

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Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 3 & Iss: 2

Case Report

Repercussions of Iatrogenic Cushing's Syndrome. About Two Cases

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Citation: Mintegui G, Mendoza M. Repercussions of Iatrogenic Cushing's Syndrome. About Two Cases. *Medi Clin Case Rep J* 2025;3(2):978-981. DOI: doi.org/10.51219/MCCRJ/Gabriela-Mintegui/256

Received: 08 June, 2025; **Accepted:** 13 June, 2025; **Published:** 16 June, 2025

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ABSTRACT

Iatrogenic, exogenous or factitious Cushing's syndrome is caused by the ingestion of synthetic glucocorticoids, which inhibit ACTH secretion and cause bilateral adrenal atrophy. It is the most common cause of hypercortisolism. It is estimated that more than 10 million Americans receive pharmacological doses of glucocorticoids each year. Therefore, exogenous Cushing's syndrome may be more common than any other cause, yet it is rarely reported1. Symptoms can be highly variable and depend on the dose and duration of glucocorticoid treatment. The most common are rounded facies, striae, muscle weakness, weight gain and metabolic repercussions such as hyperglycemia and dyslipidemia. Discontinuation of these drugs, when used chronically, should be slow and progressive to avoid adrenal insufficiency, which can lead to death. Glucocorticoid toxicity is one of the most common causes of iatrogenic illness associated with the treatment of chronic diseases. The lowest dose of glucocorticoids should be used for the shortest duration necessary to achieve treatment goals and avoid the adverse effects of these drugs.

Keywords: Cushing's syndrome; Hyperglycemia and dyslipidemia; Glucocorticoid toxicity

Introduction

Cushing's syndrome (CS) is a condition characterized by elevated cortisol levels from various causes. Iatrogenic Cushing's syndrome is caused by excessive consumption of exogenous glucocorticoids (GCs), which are typically prescribed for non-endocrine disorders. In these cases, ACTH and cortisol levels are low, as are 24-hour urinary free cortisol levels. The most common cause of iatrogenic Cushing's syndrome is the ingestion of an oral corticosteroid prescribed for various conditions. However, it can also be caused by oral, injectable, topical and inhaled GCs[2].

Estimates of the incidence of Cushing's syndrome are imprecise and likely underestimate the incidence of iatrogenic Cushing's syndrome, undiagnosed mild hypercortisolism and ectopic atrophy syndrome[3].

The symptoms and signs of hypercortisolism are a direct consequence of chronic exposure to excess GCs. There is a wide spectrum of manifestations, from subclinical to overt syndrome, depending on the duration and intensity of steroid excess. Metabolic disorders (such as obesity, high blood pressure and dysglucemia) are common in people without adrenal hyperfunction[1].

Glucocorticoids used in chronic diseases (such as prednisone or prednisolone) do not have significant mineralocorticoid

androgenic or estrogenic activity; therefore, their main adverse effects result from the inhibition of hypothalamic-pituitary-adrenal function and the development of iatrogenic Cushing's syndrome[4].

Clinical manifestations are variable and depend on the intensity and duration of hypercortisolism, its origin and the sensitivity of GC receptors. The most common are: central obesity, moon face, increased facial fat deposits, supraclavicular hollows and cervical spine (dorsal hump), depression, hypertension, prediabetes and overt diabetes, menstrual irregularities, thin skin, acne, hirsutism and wine-red striae.

More frequently, systemic glucocorticoids can cause a dose-dependent, usually mild, increase in fasting blood glucose and a greater increase in postprandial blood glucose in patients without preexisting diabetes mellitus[4].

The most common symptoms that discriminate Cushing's syndrome are: wine-red striae, facial plethora, easy bruising and proximal muscle weakness.

The diagnosis of Cushing's syndrome is based primarily on clinical suspicion based on the patient's symptoms and signs and laboratory testing is not necessary.

In exogenous CS, treatment consists of withdrawing the drug (GC) causing the hypercortisolism.

Despite their effectiveness, steroid-induced side effects generally require a gradual reduction in the drug dose as soon as the disease being treated is under control. The reduction must be done carefully to avoid both recurrent activity of the underlying disease and possible cortisol deficiency resulting from suppression of the hypothalamic-pituitary-adrenal axis during the period of steroid therapy[3].

Case Report

A 17-year-old adolescent student presents with weight gain over the past 6 months (6 kg in the last month), which has been difficult to lose despite following the eating habits prescribed by a nutritionist. She reports changes in body fat distribution, predominantly on the face, neck and abdominal girdle. Skin stretches marks on her upper limbs have changed from pearly to wine-red, increasing in number and distribution on her abdomen, breasts, armpits and, in the last month, on her lower limbs. She has frontal acne, no seborrhea or hirsutism. She denies petechiae or ecchymosis. She has no high blood pressure and is unaware of any changes in blood glucose. She has no asthenia or muscle weakness. She menarche at age 11 and has regular 30/5 menstrual cycles with oral contraceptives. She reports that she has received anti-allergy medication combined with corticosteroids (10 mg loratadine with 2 mg dexamethasone) over the past eight months. Examination: obese, weight 90 kg, height 164 cm, BMI 34 kg/m2, abdominal waist 111 cm. round face, ruddy facies, tendency to double chin **(Figure 1)**. Mild frontal acne, no seborrhea, hirsutism or acanthosis nigricans, no petechiae or ecchymosis. Red striae 7 mm to 1 cm thick in the armpits, breasts, abdomen, upper and lower limbs **(Figures 2,3)**. Blown supraclavicular fossae, dorsal hump. Prominent abdomen, striae with characteristics already described in the flank, iliac fossae and hypogastrium. No atrophy of the shoulder or pelvic girdle. Lower limbs retain muscle mass. Normal cardiovascular. Laboratory; blood glucose 108 mg/dl, lipid profile with triglycerides of 234 mg/dl, rest normal. Discontinuation of dexamethasone and recovery of the adrenal axis took 2 years in this patient.

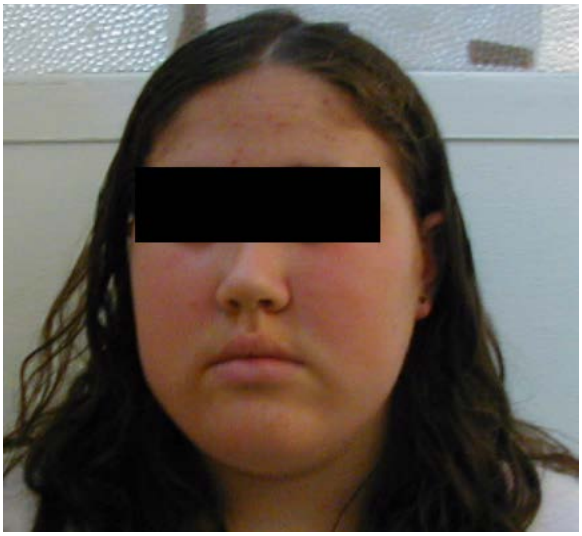

Figure 1: Round face, Ruddy facies, tendency to double chin.

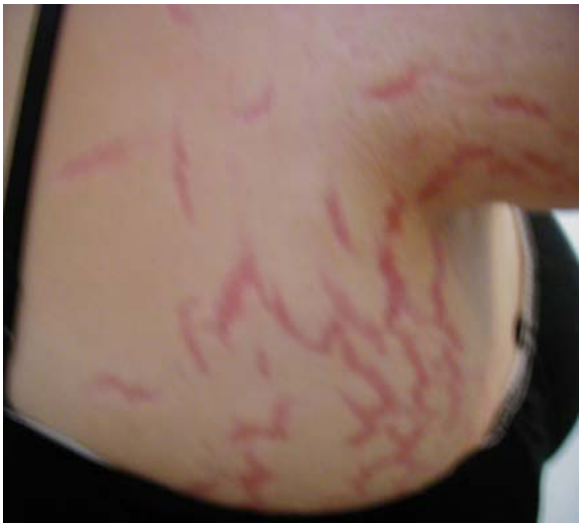

Figure 2: Upper Limb.

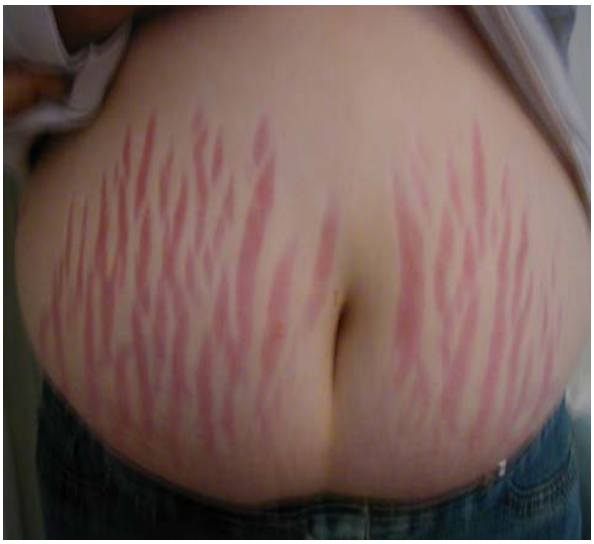

Figure 3: Lower Limb.

A 38-year-old man presented with bone pain that began in the previous 2 months; it was located mainly in the thoracolumbar spine and appeared upon rising, persisting all

day. It was moderate in intensity, non-irradiating and partially relieved with common analgesics. He reported a 6 cm loss in height over the past year. He denied paresis, plejia or altered sensation in the lower limbs. Over the past 3 months, he had noticed weight gain (15 kg at that time), predominantly in the abdomen. He had no changes in his eating habits and he performed regular aerobic exercise 3 times per week. He had red stretch marks on his abdomen, lower limbs and lower limbs. He had been receiving 10 mg of loratadine combined with 2 mg of dexamethasone daily for the past 20 years, self-medicating for skin allergies. He had no fractures. He had not received calcium, vitamin D or antiresorptive. No other medication intake. From the examination: weight 75 kg, height 174 cm, BMI 23 kg/m2, abdominal waist 106 cm. Round face, ruddy facies; acanthosis nigricans on the neck and armpits. Red striae 1 cm thick on the abdomen and limbs. Abdomen: prominent, striae. Marked increase in dorsal kyphosis, tenderness on palpation of the thoracolumbar spine that made the examination difficult. Bone densitometry of the spine and hip with VFA was requested, which showed a vertebral Z-score of -3.4 and a vertebral fracture at the L1 level. Blood glucose 112 mg/dl; total cholesterol 245 mg/dl, triglycerides 280 mg/dl, HDL 32, LDL 197 mg/dl. From ophthalmology, bilateral subcapsular cataracts. A progressive reduction in dexamethasone is initiated, which takes a year and a half to achieve corticosteroid suppression.

Discussion

Long-term effects of glucocorticoid exposure, such as atrophy of anterior pituitary and adrenal gland cells, are caused in part by the nonspecific effects of glucocorticoids on cellular function. They can cause serious adverse reactions, especially when administered in high doses for prolonged periods[5].

Once cellular atrophy occurs, full recovery from the effects of glucocorticoids may take months or even years after discontinuation[4].

The daily dose of glucocorticoids is a key factor in toxicity, with higher doses carrying a higher risk of adverse effects[6].

The side effects of corticosteroids depend on dose and duration. The daily dose used is a key factor in toxicity. Some studies suggest that very low doses of glucocorticoids (e.g., prednisone <5 mg/day) are associated with fewer adverse effects[7].

However, not everyone agrees with this assertion; others suggest adverse effects even at low doses, including hypothalamic-pituitary-adrenal (HPA) axis suppression in patients taking less than 5 mg/day of prednisone for less than four weeks and the development of cataracts[4,8].

However, higher doses produce a greater risk of adverse effects. Doses such as 1 g/day of methylprednisolone or its equivalent can cause more significant adverse effects, such as increased appetite and weight gain, gastritis, insomnia and mood swings[4].

Longer durations of GC treatment, i.e., higher cumulative doses, are associated with adverse effects. However, short-term use of corticosteroids can also be associated with serious adverse effects, particularly at higher doses[4].

Adverse effects of GCs on the skin can appear even at low doses, such as Cushingoid features, weight gain, skin thinning, striae, ecchymosis, acne, mild hirsutism and facial erythema. Striae usually develop due to a combination of skin thinning and weight gain. These elements appear in both cases, but were clearly more noticeable in case 1, although she received corticosteroids for a shorter period of time. This speaks to the hypothesis that the effects of these drugs also depend on the idiosyncrasies of each individual. Acne (occurring in 2% to 19% of patients), hirsutism (occurring in 5% to 8% of patients) and facial plethora were also very noticeable in case 1 but not in case 2[4]. Some adverse effects, such as decreased bone mineral density or early cataracts, may be asymptomatic until later complications develop, such as vertebral fracture or cataract requiring surgical removal[4]. In case 2, both alterations appeared, which is logical because the patient was on glucocorticoid treatment for two decades. Many adverse effects of GCs are at least partially reversible over time after discontinuation, with the exception of cataracts, atherosclerotic vascular disease and bone effects (osteoporosis and osteonecrosis).

Hyperglycemia was detected in both cases. The mechanism by which glucocorticoids cause hyperglycemia is multifactorial and includes increased hepatic gluconeogenesis, inhibition of glucose uptake in adipose tissue and alteration of receptor and post receptor functions[4].

Glucocorticoid-induced hyperglycemia improves with dose reduction and is generally reversed upon discontinuation of the medication, although persistent diabetes develops in some cases[9]. The cumulative dose of oral glucocorticoids was associated with a higher incidence of hypertension. Incidence rates increased with higher cumulative glucocorticoid doses[10].

GCs were associated with a duration- and dose-dependent increased risk of major adverse cardiovascular events[11], as well as with a nearly twofold increased risk of atrial fibrillation or flutter[12].

In case 2, subcapsular cataracts were detected. These are one of the described effects and often appear after prolonged use of glucocorticoids, even at very low doses. As in this patient, they are usually bilateral and develop slowly, usually appearing in a posterior subcapsular area[4]. Although the minimum dose to cause this complication is unclear, it is considered that it may occur with treatment lasting more than one year. For these reasons and to avoid complications from chronic GC use, recommendations have been made to evaluate and treat conditions such as diabetes mellitus and prediabetes, hypertension, heart failure, obesity and overweight, cataracts or glaucoma, low bone density or osteoporosis[13].

Adverse reactions due to withdrawal are a major challenge in long-term glucocorticoid withdrawal. Due to the suppression of the hypothalamic-pituitary-adrenal axis, this leads to potentially life-threatening adrenal insufficiency, which can become symptomatic upon discontinuation of treatment[5]. In both cases, recovery of the HPA axis took more than a year because the gradual rate of dose reduction was very slow. Each reduction in corticosteroid dose produced numerous symptoms due to glucocorticoid withdrawal syndrome, which led both patients to abandon their daily activities and sometimes to increase the corticosteroid dose[14].

The suggestion is that, if symptoms prevent discontinuation of treatment, an HPA axis test should be performed to detect adrenal insufficiency[5]. In both cases, a post-ACTH cortisol test was performed to certify the axis's integrity.

Treatment of Cushing's syndrome with exogenous therapy consists of discontinuing the glucocorticoid. Most patients who have taken glucocorticoids long enough to cause Cushing's syndrome will experience a period of hypothalamic-pituitary-adrenal insufficiency upon discontinuation of treatment. Therefore, gradual withdrawal is necessary[5].

Conclusion

Exogenous glucocorticoid administration can suppress the hypothalamic-pituitary-adrenal axis. Abrupt discontinuation or rapid withdrawal of glucocorticoids can cause symptoms of adrenal insufficiency and their resolution is challenging.

When using these drugs, it is ideal to administer doses sufficient to control the disease in the shortest possible time to minimize adverse effects.

Preexisting comorbid conditions that may increase risk should be assessed and management of these conditions should be optimized.

We must be vigilant because some patients with adrenal insufficiency require physiological doses of glucocorticoids, which may be lifelong if the HPA axis does not recover.

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