

# Exogenous Cushing's syndrome with a difficult diagnosis

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## Abstract

**Introduction:** Cushing's syndrome (CS) is a group of signs and symptoms caused by chronic exposure to excessive glucocorticoids. The use of medications containing glucocorticoids is the most common cause, but they may be hidden in some products sold as nutritional supplements or naturopathic medications, which makes the diagnostic approach more difficult.

**Case presentation:** this was a 40-year-old patient with typical clinical signs of Cushing's syndrome and discordant results of diagnostic tests to identify its origin. It was ultimately determined that the patient had been chronically taking a "naturopathic" product known as artrin®, which was analyzed in the institution's lab and found to contain cortisol.

**Conclusion:** chronic exposure to exogenous glucocorticoids, whether surreptitious, unknown or prescribed, causes CS and should be promptly distinguished from endogenous forms to avoid inappropriate diagnostic tests and treatments. (*Acta Med Colomb* 2020; 45. DOI: <https://doi.org/10.36104/amc.2020.1500>).

**Key words:** *Cushing's syndrome, exogenous glucocorticoids, herbal supplements.*

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## Introduction

Cushing's syndrome (CS) is a rare disease with an incidence of two to three cases per million people per year, but with a high morbidity and mortality (1). It is caused by prolonged and inappropriate exposure to excessive glucocorticoids. The presence of physical signs such as moon face, truncal obesity, purple striae, hirsutism and acne, as well as related metabolic complications like diabetes, arterial hypertension and osteoporosis, should raise a suspicion of hypercortisolism. However, the diagnosis is almost always a clinical challenge.

There are two types of Cushing's syndrome: endogenous and exogenous. Endogenous Cushing's syndrome may be ACTH dependent, constituting 80-85% of cases, arising in most cases from an ACTH-secreting pituitary adenoma, or caused by ectopic secretion of ACTH or of corticotropin-releasing hormone (CRH) in certain pulmonary or pancreatic neuroendocrine tumors. ACTH-independent Cushing's syndrome makes up 15-20% of endogenous hypercortisolism cases and is a result of adrenal adenomas or carcinomas (2-4).

Exogenous Cushing's, which is the main cause of hypercortisolism, is a consequence of prolonged exposure to medications with a glucocorticoid effect. Generally, it

is transient and resolves when exposure is discontinued. However, when products with hidden glucocorticoids are used, it may become a chronic disease which is difficult to diagnose (5).

## Clinical case

A 40-year-old patient with a history of psoriatic arthritis from the age of 30, who developed physical changes with central obesity, purple abdominal striae and a moon face a year prior to this consult, associated with brittle diabetes mellitus and severe arterial hypertension. He was studied in his usual place of residence, with a finding of hypercortisolism. The patient repeatedly denied taking glucocorticoid drugs.

He was referred to the Instituto Nacional de Cancerología with a diagnosis of ACTH-dependent Cushing's syndrome, with pituitary imaging negative for adenomas. The biochemical tests were repeated on the initial exam (Table 1), as their results were not congruent. The institutional lab results are also shown in Table 1, with findings indicative of ACTH-independent Cushing's syndrome. A tomography of the suprarenal glands was normal.

Subsequently, on a second visit, the patient's basal cortisol was suppressed, which led to a suspicion of surreptitious ingestion of glucocorticoids. The patient

reported taking a “naturopathic” product sold as artrin® intermittently for more than 12 months, with three to four-month periods of constant use, and periods of up to two weeks with no use. Artrin® is a product sold in Colombia without an INVIMA [Translator’s note: drug and food regulation agency] license (6). However, the label does not mention glucocorticoids as one of its ingredients, as shown in Figure 1. Due to the time coincidence between artrin® consumption and the clinical picture and the lack of information regarding its contents in official sources (INVIMA), we conducted a cortisol measurement test on a tablet of artrin®. For this test, one tablet was dissolved in 5 cc of normal saline solution and an aliquot was taken, which was processed in our institution’s clinical laboratory using the first generation Elecsys cortisol assay (Roche® Diagnostics) with a result greater than 1,352 nmol/L (chemiluminescence, range <5-1,352 nmol/L).

The patient was instructed to discontinue use of the «naturopathic» product and, to avoid adrenal insufficiency due to axis suppression, the patient received oral prednisolone replacement at 5 mg/day, with gradual dose reduction until it was completely withdrawn at six weeks. The patient experienced progressive improvement of the physical characteristics of Cushing’s and complete correction of the hyperglycemia, although arterial hypertension persisted.

## Discussion

Cushing’s syndrome (CS) is a group of signs and symptoms caused by chronic exposure to excessive glucocorticoids. In the initial diagnostic approach to any patient with clinical signs of hypercortisolism, it is imperative to rule out the use of glucocorticoid-containing medications. These drugs are commonly prescribed for oral, parenteral, topical, rectal or inhaled use. Patients receiving pain-control injections may not be aware that they have received a potent glucocorticoid. Glucocorticoids may also be present in a variety of over-the-counter medications. Recently, the use of skin whitening creams and their association with Cushing’s syndrome has been reported (7).

Some products sold without a prescription mention containing plant extracts with analgesic and anti-inflammatory properties. While bromelia extracts containing flavonoid glycosides may have anti-inflammatory properties (8), as may *Boswellia serrata* extracts (9), in the case of the ar-

trin® product used by the patient, we inferred that it was a fraudulent product, since the label had an incorrect list of the plant extracts it claimed to contain, and especially since glucocorticoid content was proven by cortisol detection on the clinical laboratory test.

When a patient who uses this type of product develops Cushing’s syndrome characteristics, measurement of synthetic steroids in blood or urine is recommended (10). However, lab tests to determine the concentrations of these synthetic steroids are not available in our setting. Thus, we depend on synthetic glucocorticoids such as prednisolone, prednisone and methylprednisolone cross-reacting with the plasma and urine cortisol test using immunoassay methods as shown in Table 2. By contrast, dexamethasone causes little or no cross-reaction with cortisol in analytical assays, which justifies its use as the diagnostic screening test for Cushing’s syndrome known as the low-dose dexamethasone suppression test (11).

Based on the test results, we suspected that artrin® contained one of the three synthetic steroids mentioned. However, for INVIMA, artrin® is a product whose legitimate composition is unknown (6).

The discrepancy between the serum cortisol and ACTH tests seen in this patient was explained by the intermittent use of artrin® and the use of different analytical methods for the various measurements.



Figure 1. Packaging and label of the artrin® product.

Table 1. Patient’s clinical laboratory tests.

Month	Cortisol A.M	ACTH A.M	LDDST Cortisol	24-hour urine cortisol (ug/24 h)
August 2008 (external)	9.0	82	3.9	308 (RV 32-243)
November 2008 (INC)	8.07	Less than 1	10.9	ND
March 2009 (INC)	3.4	ND	ND	ND

ND: No data LDDST: Low-dose dexamethasone suppression test.

**Table 2.** Cross-reactivity in immunoassays for cortisol.

Synthetic steroids	Cross-reactivity on the cortisol test	
	By chemiluminescence (I2)	By ELISA enzyme immunoassay (I3)
Methylprednisolone	26%	249%
Prednisolone	109%	148%
Prednisone	39%	0.3%
Dexamethasone	0.2%	NR

NR: Not reported

## Conclusion

Chronic exposure to exogenous glucocorticoids should be ruled out early in any patient suspected of having Cushing's syndrome, and "naturopathic medications" should be considered, especially those with "anti-inflammatory and analgesic properties," since they may contain hidden synthetic steroids.

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