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Betamethasone induced Iatrogenic Cushing's Syndrome in a patient with Systemic Lupus Erythematosus: A Case Report

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Abstract

Background:
Cushing's syndrome (CS) is a disorder characterized by prolonged exposure to elevated glucocorticoid levels. Exogenous or iatrogenic CS is the most common form, frequently associated with long-term corticosteroid therapy, particularly in autoimmune diseases such as systemic lupus erythematosus (SLE).

Case Summary:
We report a case of a 72-year-old female with a history of SLE and hypertension who developed iatrogenic Cushing's syndrome following 2–3 months of oral betamethasone therapy. She presented with progressive weight gain, moon facies, truncal obesity, and fatigue. Diagnostic tests confirmed ACTH-independent hypercortisolism with suppressed ACTH levels. Imaging ruled out endogenous etiologies. A structured tapering and withdrawal of betamethasone, along with optimization of azathioprine and initiation of hydroxychloroquine, led to a gradual reversal of Cushingoid symptoms and stabilization of her SLE.

Conclusion:
This case underscores the need for cautious glucocorticoid use and highlights the utility of steroid-sparing agents in preventing iatrogenic complications. Early recognition and dechallenge are crucial for recovery of HPA axis function and effective autoimmune disease management.

Keywords: *Iatrogenic Cushing's syndrome, betamethasone, systemic lupus erythematosus, glucocorticoid tapering, steroid-sparing agents, adverse drug reaction.*

I. Introduction

Cushing's syndrome (CS) refers to a constellation of clinical manifestations resulting from chronic exposure to elevated levels of glucocorticoids, whether of endogenous or exogenous origin. Endogenous CS is generally classified into ACTH-dependent forms—primarily pituitary adenomas (Cushing's disease)—and ACTH-independent types, which include cortisol-producing adrenal tumors or hyperplasia [1] [2]. In contrast, exogenous or iatrogenic CS is caused by prolonged administration of synthetic glucocorticoids and is considered the most prevalent subtype in clinical practice, especially among patients undergoing long-term corticosteroid therapy for inflammatory or autoimmune diseases [3] [4].

The clinical presentation of CS is highly variable but typically includes central (truncal) obesity, moon facies, dorsocervical fat pad ("buffalo hump"), purple striae, hypertension, glucose intolerance, hirsutism, proximal myopathy, and psychiatric symptoms [1] [5] [6]. Diagnostic evaluation involves confirming cortisol excess using tests such as 24-hour urinary free cortisol, low-dose dexamethasone suppression, and late-night salivary cortisol levels. Once hypercortisolism is established, further testing is needed to determine whether the etiology is ACTH-dependent or ACTH-independent [2] [7]. Imaging modalities such as pituitary MRI or adrenal CT scans are crucial for identifying endogenous causes, whereas a history of glucocorticoid use may point toward an iatrogenic origin. Management of iatrogenic CS typically includes gradual tapering of corticosteroids to restore HPA axis function, with supportive care for metabolic and cardiovascular complications [4] [8].

Steroid-induced Cushing's syndrome accounts for up to 80% of all CS cases in some cohorts, highlighting the widespread impact of therapeutic glucocorticoid use [4] [9] [10]. Despite its frequency, exogenous CS is frequently underdiagnosed due to overlapping [6] [9] symptoms with underlying diseases, and delayed diagnosis can exacerbate patient morbidity. This underscores the importance of clinical vigilance when evaluating patients on long-term steroids.

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that often necessitates immunosuppressive therapy to control systemic inflammation and prevent end-organ damage. Glucocorticoids remain a mainstay in SLE treatment, particularly during flares or severe manifestations [11] [12]. Betamethasone, a potent long-acting corticosteroid, may be employed for its strong anti-inflammatory effects, although its high glucocorticoid potency increases the risk of HPA axis suppression and iatrogenic CS, especially with prolonged use [3] [12] [13]. According to the 2023 EULAR guidelines, glucocorticoids should be used only as a short-term "bridging" therapy in SLE, with a target maintenance dose of ≤5 mg/day (prednisone equivalent), and withdrawal should be attempted when possible [12]. Failure to adhere to these guidelines increases the risk of steroid-induced complications, particularly in patients with additional risk factors.

The following case describes a young female with SLE who developed iatrogenic Cushing's syndrome after 2–3 months of betamethasone therapy, underscoring the diagnostic challenge and clinical consequences of steroid overuse in autoimmune disease management.

Case Presentation

A 72-year-old female with a 20-year history of well-controlled hypertension and a 3-year history of systemic lupus erythematosus (SLE) presented to the outpatient department (OPD) for routine blood pressure monitoring. She was on lisinopril 20 mg once daily for hypertension and had been prescribed azathioprine 25 mg, naproxen 500 mg, and betamethasone 4 mg daily for SLE management. Her SLE was primarily cutaneous and musculoskeletal, with no major organ involvement reported in prior visits.

During the consultation, the patient expressed concern about progressive changes in her appearance, particularly over the past 4–5 months. She described facial rounding, a moon-shaped, puffy face, and noticeable central weight gain, particularly around the abdomen and upper back. She reported an unintended weight gain of 8 kg over the past 3–4 months, despite no significant changes in appetite or activity level. On further questioning, she also noted easy bruising, fatigue, and mild proximal muscle weakness, which she initially attributed to aging and her autoimmune condition.

On physical examination, her blood pressure was 138/84 mmHg, and she had central obesity, facial fullness (moon facies), a buffalo hump, and thin skin with a few ecchymotic patches on her forearms. There was no evidence of SLE flare or active joint inflammation.

Given the chronic use of systemic corticosteroids and the development of classic Cushingoid features, iatrogenic Cushing's syndrome was suspected. The following tests were ordered:

- 24-hour urinary free cortisol (UFC)
- Low-dose overnight dexamethasone suppression test (1 mg dexamethasone at 11 p.m., cortisol measured at 8 a.m.)
- Late-night salivary cortisol levels
- Morning serum cortisol and ACTH levels

Laboratory results revealed elevated 24-hour urinary free cortisol, failure to suppress serum cortisol after the dexamethasone test, and suppressed ACTH, confirming a diagnosis of exogenous (ACTH-independent) Cushing's syndrome. Imaging studies, including abdominal CT and pituitary MRI, were unremarkable, effectively ruling out endogenous causes such as adrenal adenoma, pituitary microadenoma, or ectopic ACTH-producing tumors.

Upon diagnosis, a dechallenge was performed by gradually tapering and then discontinuing betamethasone**.** The patient was transitioned to Hydroxychloroquine 200 mg/day and the azathioprine dose was optimized to 50 mg/day for continued SLE control. Naproxen was stopped**,** and non-pharmacological measures including dietary counseling, weight management**,** and physical activity were initiated.

Causality assessment of the adverse drug reaction (ADR) was performed using standard scales revealing probable on WHO probability scale, Naranjo scale as well as Karch and Lasagna's scale. The severity of the ADR was categorized using the Modified Hartwig and Siegel Severity Assessment Scale, where the case was rated as Level 4b (Moderate) indicating that the reaction required therapeutic intervention and led to a change in the drug regimen. Over the next 3 months, the patient demonstrated gradual improvement in Cushingoid features, with a 2.5 kg weight reduction, improved facial contour, and reduced fatigue. Repeat cortisol levels began to normalize, indicating partial recovery of HPA axis function.

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Figure 1: Naranjo Scale (NOTE- this image should appear at the end of case presentation.)
Adapted from: https://www.robsonforensic.com/articles/adverse-drug-reactions-expert-article

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	2
6. Did the reaction reappear when a placebo was given? *	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
			Total Score:	7

Question 6 refers to a typical clinical trials situation and is included here for completeness.

Total Score	Interpretation of Scores
≥ 9	Definite. The reaction (1) followed a reasonable temporal sequence after drug exposure had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, (3) was confirmed by improvement on withdrawing the drug and (4) reappeared on reexposure.
5 - 8	Probable. The reaction (1) followed a reasonable temporal sequence after a drug exposure, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
1 - 4	Possible. The reaction (1) followed a temporal sequence after a drug exposure, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
≤ 0	Doubtful. The reaction was likely related to factors other than a drug.

The Naranjo scale is a tool to help clarify how to evaluate a potential causal association. It is not intended to solve all the complex problems of identification and classification of ADRs.

II. Discussion

Cushing's syndrome caused by exogenous glucocorticoids—termed iatrogenic Cushing's syndrome (ICS)—is the most frequently encountered variant of CS in clinical practice. It develops when high doses of synthetic glucocorticoids such as betamethasone are used for extended periods, leading to suppression of endogenous cortisol production via inhibition of the hypothalamic-pituitary-adrenal (HPA) axis [14] [15]. Unlike endogenous CS, which may result from pituitary ACTH overproduction (Cushing's disease) or adrenal tumors, ICS arises purely from pharmacologic administration of corticosteroids and lacks autonomous hormone production [14] [16].

Glucocorticoids suppress the HPA axis through both rapid and delayed feedback mechanisms. At the central level, exogenous steroids bind to glucocorticoid receptors in the hypothalamus and anterior pituitary, thereby inhibiting the secretion of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), respectively. This results in decreased adrenal stimulation and cortisol synthesis [15]. Rapid feedback occurs within minutes through nongenomic pathways that involve membrane-bound receptors and retrograde endocannabinoid signaling in the paraventricular nucleus (PVN) of the hypothalamus [15]. Slower, genomic mechanisms inhibit CRH and ACTH gene expression over hours to days, perpetuating adrenal atrophy with prolonged glucocorticoid exposure [14] [17].

This suppression becomes clinically significant when patients are weaned off glucocorticoids or experience physiological stress, as the atrophic adrenal glands are unable to mount an appropriate cortisol response—leading to secondary adrenal insufficiency. This condition can range from fatigue and hypotension to life-threatening adrenal crisis, especially in the absence of gradual tapering [14] [18].

In SLE management, corticosteroids play a pivotal role in controlling inflammation, particularly during disease flares. Betamethasone, owing to its

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high potency and long half-life, is effective but also carries a higher risk of iatrogenic complications like ICS when used beyond short-term protocols [13] [19]. According to the 2023 EULAR recommendations, glucocorticoids should be prescribed at the lowest effective dose (≤5 mg/day prednisone equivalent) and discontinued when disease activity permits. Long-term steroid use is associated with significant cumulative toxicity, including metabolic syndrome, osteoporosis, cardiovascular disease, and Cushingoid changes [7] [16].

Management of ICS in SLE patients involves a gradual tapering protocol tailored to the individual's steroid history and disease activity. Tapering allows the HPA axis to regain responsiveness and resume endogenous cortisol production [14] [20]. A common strategy is to reduce the dose slowly over weeks to months, especially when transitioning from supraphysiological doses. Monitoring morning serum cortisol or conducting an ACTH stimulation test can help assess adrenal recovery [14] [18].

Table 1: Suggested Tapering Strategy for Moderate- to Long-term Steroid Use (NOTE- this table should appear after 5th paragraph in discussion.)

Initial Dose (Prednisone Equivalent)	Tapering Step	Interval
≥20 mg/day	Reduce by 5 mg	Every 1–2 weeks
10–20 mg/day	Reduce by 2.5 mg	Every 2 weeks
≤10 mg/day	Reduce by 1 mg	Every 2–4 weeks
Final phase (≤5 mg/day)	Switch to morning dosing, monitor cortisol	Taper slowly

To maintain SLE remission during steroid tapering, steroid-sparing agents such as hydroxychloroquine, azathioprine, methotrexate, or biologic agents like belimumab and anifrolumab are recommended. These therapies allow better long-term disease control with reduced reliance on glucocorticoids [17] [21]. Recent studies also suggest that short pulses of intravenous methylprednisolone (MP) can rapidly suppress flares through nongenomic pathways, allowing earlier steroid withdrawal without loss of disease control [21] [22].

In this case, tapering betamethasone combined with supportive therapy and initiation of steroid-sparing drugs resulted in reversal of Cushingoid features and stabilization of lupus symptoms. This highlights the critical need for judicious steroid use, early tapering, and integration of immunosuppressive alternatives in autoimmune disease management to minimize adverse effects and support adrenal recovery.

III. Conclusion

This case highlights the clinical significance of vigilant monitoring in patients receiving prolonged corticosteroid therapy, especially in the context of autoimmune diseases such as systemic lupus erythematosus. Betamethasone, although effective in controlling SLE flares, poses a high risk of iatrogenic Cushing's syndrome when used beyond short-term regimens. Prompt recognition of Cushingoid features, appropriate diagnostic evaluation, and a structured dechallenge can lead to favorable outcomes. This report reinforces the importance of adhering to steroid-sparing strategies and tapering protocols as outlined in current clinical guidelines to minimize steroid-related morbidity while maintaining disease control in SLE.

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