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CASE REPORT

Glucocorticoid-induced adrenal insufficiency after receiving intravenous methylprednisolone for Graves' ophthalmopathy: a case report

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ABSTRACT

BACKGROUND
Graves' ophthalmopathy (GO) is the most common extrathyroidal manifestation of Graves' disease and can significantly impair visual function and quality of life. High-dose intravenous methylprednisolone (IVMP) is recommended as first-line therapy for moderate-to-severe active GO due to its superior efficacy and tolerability compared with oral glucocorticoids. However, IVMP therapy may be associated with rare but potentially serious adverse effects, including suppression of the hypothalamic–pituitary–adrenal (HPA) axis leading to GI adrenal insufficiency (GI-AI).

CASE DESCRIPTION
We report the case of a 38-year-old man with Graves' disease who developed AI following IVMP therapy for moderate-to-severe GO. The patient received five weekly doses of IVMP 500 mg (cumulative dose 2.5 g) for progressive ocular symptoms. He subsequently presented with fatigue, weight gain, moon face, and buffalo hump. Laboratory evaluation revealed a markedly low morning serum cortisol level of 1 mcg/dL, confirming adrenal insufficiency. Patient was diagnosed with GI-AI accompanied by features of iatrogenic Cushing's syndrome. Management consisted of hydrocortisone replacement therapy at a dose of 20 mg/day along with ongoing antithyroid treatment using methimazole. Serial monitoring of cortisol levels demonstrated gradual recovery of HPA axis function, accompanied by clinical improvement.

CONCLUSION
This case highlights that glucocorticoid-induced adrenal insufficiency can occur on IVMP used for GO. Clinicians should maintain a high index of suspicion and perform appropriate adrenal function monitoring during and after IVMP therapy to ensure early detection and safe management of this potentially life-threatening complication.

Keywords: Graves' ophthalmopathy, adrenal insufficiency, intravenous glucocorticoid, HPA axis, methylprednisolone

INTRODUCTION

Graves' ophthalmopathy (GO) is the most common extrathyroidal manifestation of Graves' disease, occurring in 25–50% of patients and characterized by orbital inflammation, eyelid retraction, proptosis, and, in severe cases, optic nerve compression.[1,2] The pathogenesis involves complex autoimmune mechanisms where autoantibody-mediated inflammation targets orbital fibroblasts, adipocytes, and extraocular muscles, resulting in a self-perpetuating cycle of cytokine release, tissue expansion, and fibrosis, with clinical manifestations ranging from mild ocular surface disease to sight-threatening dysthyroid optic neuropathy.[3] The condition may significantly impair quality of life and, if untreated, lead to sight-threatening complications.

High-dose intravenous methylprednisolone (IVMP) is the first-line therapy for moderate-to-severe GO because of its superior efficacy and tolerability compared with oral glucocorticoids (GC).[4,5] Recent systematic reviews confirm that intravenous GC remain the cornerstone of management for active moderate-to-severe GO, though combination approaches with immunosuppressive agents and emerging targeted biologics are increasingly being evaluated to improve clinical activity scores and quality of life outcomes.[6] However, pulse IVMP therapy may be complicated by adverse effects, including hepatotoxicity, cardiovascular events, and hypothalamic-pituitary-adrenal (HPA) axis suppression. Among these, glucocorticoid-induced adrenal insufficiency (GI-AI) is considered rare but clinically important, as it can be life-threatening if unrecognized.[7]

Glucocorticoid-induced AI represents a significant yet under-recognized complication of therapeutic GC use, although the specific incidence following pulse IVMP therapy for GO has not been comprehensively characterized.[8] Current evidence emphasizes that HPA axis suppression risk is influenced by multiple factors including treatment duration, cumulative dose, GC potency, and individual patient susceptibility, highlighting the critical importance of individualized monitoring strategies and appropriate patient counseling regarding adrenal crisis prevention during and after GC therapy.[9]

Here, we report the case of a 38-year-old man with GO who developed AI following pulse IVMP therapy. This case highlights the importance of monitoring adrenal function during and after high-dose GC treatment.

CASE REPORT

A 38-year-old male presented with a two-week history of weakness and progressive facial swelling, accompanied by a weight gain of 3 kg. He had been diagnosed with Graves' disease two years earlier and was on regular follow-up. Due to worsening ocular symptoms over the past two months, he was referred to Dr. M. Djamil General Hospital. He had been receiving thiamazole 10 mg daily; propranolol had been discontinued. Based on ophthalmology consultation, intravenous methylprednisolone (500 mg weekly) was initiated for five weeks starting in August 2024.

On examination, the patient had buffalo hump and moon face. Blood pressure was 120/80 mmHg and heart rate 62 bpm. Thyroid enlargement, retrobulbar pain, pain on eye movement, and caruncle inflammation were noted, without vision-threatening complications. Hertel exophthalmometry measured 22 mm bilaterally (normal: 10–18 mm).

Laboratory tests showed suppressed TSH and elevated free thyroxine (FT4) before admission. At our center, results included thyrotropin receptor antibodies (TRAb) 30.5 (normal <1.75), FT4 16.85 pmol/L, TSH 0.02 µIU/mL, fasting plasma glucose 118 mg/dL, 2h-postprandial glucose 89 mg/dL, and HbA1c 6.0%**.** Thyroid ultrasonography demonstrated bilateral diffuse thyroid enlargement without nodules. Repeat testing in October 2024 revealed low morning cortisol (1 mcg/dL; normal 3.7–19.4), consistent with GI- AI, with concomitant reduction of FT4 and persistent TSH suppression.

The patient was diagnosed with Graves' disease, moderate-to-severe GO with grade 3 NOSPECS (this acronym standing for No signs or symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle involvement, Corneal involvement, and Sight loss), clinical activity score **(**CAS) 3/7, GI-AI, iatrogenic Cushing's syndrome, and prediabetes. He was treated with thiamazole 10 mg once daily and hydrocortisone 20 mg once daily. Follow-up monitoring of cortisol and thyroid function was planned. At subsequent visits, symptoms of fatigue improved and morning cortisol levels gradually increased, indicating partial recovery of HPA axis function. Consent was obtained from the

patient for the publication of this article and any accompanying images.

DISCUSSION

This case highlights the clinical challenges of managing thyroid eye disease (TED), particularly GO, which remains one of the most debilitating extrathyroidal manifestations of Graves' disease. The noteworthy aspect of this case lies in the development of GI-AI following high-dose intravenous methylprednisolone (IVMP) therapy for moderate-to-severe TED. The main problem addressed in this case is the balance between the efficacy of IVMP as first-line therapy and the risk of hypothalamic–pituitary–adrenal (HPA) axis suppression.

The activity of TED is assessed using the clinical activity score (CAS), where a score of ≥3 or progressive symptoms indicate active TED.[2] In this patient, symptoms included retrobulbar pain, pain with eye movement, eyelid swelling, and conjunctival edema. Based on severity, the patient was classified as moderate-to-severe TED, which corresponds to NOSPECS grade 3. High-dose systemic glucocorticoids are the mainstay of treatment for such cases. Intravenous administration is preferred due to higher efficacy (70–80%) compared with oral glucocorticoids (50%) and enhanced tolerability.[2]

According to the guidelines, the recommended regimen is either 500 mg IVMP weekly for 6 weeks followed by 250 mg weekly for 6 weeks (cumulative dose 4.5 g) or 500 mg IVMP daily for 3 consecutive days monthly (cumulative dose ≤8 g).[1] In the present case, the patient received 500 mg IVMP weekly for five weeks, after which biochemical testing revealed low morning cortisol (1 mcg/dL), confirming glucocorticoid-induced AI. This highlights the fact that even within recommended regimens, suppression of adrenal function may occur and requires vigilance.

A systematic literature search revealed limited but growing documentation of GI-AI following IVMP therapy for GO. We identified four relevant prospective studies and case series published within the past decade that systematically evaluated HPA axis function in GO patients receiving IVMP.

Jespersen et al.[7] prospectively evaluated 12 GO patients receiving the standard European Group on Graves' orbitopathy (EUGOGO) protocol (cumulative dose 4.5 g) and found that all patients maintained intact HPA axis function at treatment cessation, with no cases of AI being detected by ACTH stimulation testing. This landmark study initially suggested that IVMP was relatively safe regarding adrenal suppression. Ambroziak et al.[10] evaluated 20 patients receiving the same EUGOGO protocol followed by oral prednisone taper and found that while IVMP alone did not cause AI, subsequent oral GC therapy resulted in AI in some patients, emphasizing the cumulative risk. Pelewicz et al. [11] studied 14 patients receiving 4.5 g cumulative IVMP followed by three months of oral prednisone and documented one case (7.1%) of secondary AI specifically after the oral prednisone phase, along with significant DHEA-S suppression in multiple patients. Most recently, Pelewicz and Miśkiewicz[12] conducted the first study using sensitive low-dose (1 μg) ACTH stimulation testing in 21 GO patients receiving either 4.5 g or 7.5 g cumulative IVMP. They documented that 2 of 21 patients (9.5%) developed GI-AI as defined by failure to achieve cortisol levels of ≥18.1 μg/dL during the low-dose test.

Table 1 compares these published studies with our case. Our patient is notably unique for developing clinically significant AI (morning cortisol 1.0 mcg/dL) at the lowest cumulative dose (2.5 g) reported in the literature, representing only half the standard dose in the EUGOGO protocol and substantially less than the doses in all published studies. This suggests that individual susceptibility plays a critical role independent of cumulative dose. Unlike most reported cases where AI was detected retrospectively or through systematic screening, our patient presented with overt Cushingoid features (moon facies, buffalo hump, weight gain) that prompted timely endocrine evaluation, facilitating early diagnosis. Nonetheless, AI remains a relevant clinical concern because its symptoms (fatigue, nausea, abdominal pain) are nonspecific and may overlap with GC withdrawal.[13,14]

Glucocorticoids exert their immunosuppressive effects via genomic and non-genomic pathways, including inhibition of nuclear factor kappa B (NF-κB) and modulation of cytokine transcription.[15] Long-term use, however, risks Cushing's syndrome, adrenal suppression, and infection reactivation.[1] Our patient additionally developed clinical features of iatrogenic Cushing's syndrome, further underscoring the dual complications of high-dose GC therapy.

Table 1. Comparison of published studies on adrenal insufficiency following IVMP therapy for Graves' ophthalmopathy

Authors	Study design	Sample size	IVMP protocol	Cumulative dose	Additional oral GC	AI incidence
Jespersen et al.[7]	Prospective cohort	12	Standard EUGOGO (500mg weekly×6 then 250mg weekly×6)	4.5 g	No	0/12 (0%)
Ambroziak et al.[10]	Prospective cohort	20	Standard EUGOGO	4.5 g	Yes (prednisone 30mg/day taper)	AI only after oral GC phase
Pelewicz et al.[11]	Prospective cohort	14	Standard EUGOGO	4.5 g	Yes (3 months oral prednisone)	1/14 (7.1%) after oral GC
Pelewicz & Miśkiewicz [12]	Prospective cohort	21	Standard or high-dose EUGOGO	4.5 g or 7.5 g	No	2/21 (9.5%)

Note**:** IVMP = intravenous methylprednisolone; AI = adrenal insufficiency; EUGOGO = European Group on Graves' Orbitopathy; GC = glucocorticoid

Management in this case required initiation of hydrocortisone replacement while tapering glucocorticoids, with gradual recovery of HPA axis function on follow-up. This reinforces the importance of monitoring cortisol levels during and after IVMP therapy, especially when patients develop nonspecific symptoms such as fatigue and weakness.

This report adds value by demonstrating that GI-AI is not merely a theoretical concern but a documented complication in patients with GO treated with IVMP. It emphasizes the need for individualized tapering strategies, regular endocrine monitoring, and heightened awareness of adrenal suppression, thereby contributing to safer clinical practice in the management of GO.

CONCLUSIONS

Intravenous methylprednisolone is recommended as the first-line therapy for moderate-to-severe Graves' ophthalmopathy, but this case highlights that adrenal insufficiency, although uncommon with standard regimens, may still occur. Careful clinical observation and timely evaluation of adrenal function are essential to ensure safe and effective management.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

YPE contributed to conceptualization, data collection, case analysis, manuscript drafting, and final approval of the manuscript. DA was involved in data interpretation, literature review, manuscript drafting, and critical revision. ED provided supervision, clinical insights, and critical revision. All authors have read and approved the final manuscript

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Data Availability Statement

The data supporting the findings of this study can be obtained from the corresponding author upon request.

Declaration of Use of AI in Scientific Writing

Nothing to declare.

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