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Itraconazole Treatment Unmasking Secondary Adrenal Insufficiency in a Case of Burnt-out Acromegaly

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Abstract

Adrenal insufficiency is a serious condition marked by inadequate production of steroid hormones, leading to a range of systemic symptoms and potential complications if left unrecognized. It can be categorized as primary, where pathology lies in adrenal glands themselves, or secondary, stemming from lack of adrenocorticotropic hormone-mediated stimulation from the pituitary gland. Various factors, including infection, stress, and certain medications, can precipitate or worsen adrenal insufficiency in susceptible patients. Azole antifungals have been known to interfere with adrenal hormone production and have been linked to cases of adrenal insufficiency. This case report presents a detailed scenario in which an adrenal crisis was precipitated by the use of itraconazole in a patient with no history of adrenal insufficiency, illustrating the complex interaction between medication effects and underlying endocrine issues.

Keywords
- adrenal insufficiency
- acromegaly
- empty sella
- IGF-1
- itraconazole

Introduction

Adrenal insufficiency is a potentially life-threatening condition characterized by the inadequate production of glucocorticoids, mineralocorticoids, or both, leading to a variety of symptoms, including fatigue, abdominal pain, hypotension, and electrolyte imbalances.[1,2] One of the rare but notable causes of primary adrenal insufficiency is a drug-induced adrenal insufficiency, which can occur with the azole group of antifungals, etomidate, mitotane, and metyrapone.[3]

Itraconazole, a triazole antifungal agent commonly used to treat fungal infections, is known to inhibit human steroidogenesis cytochrome P450 enzymes including the cholesterol side-chain cleavage complex 17,20-lyase, 11β-hydroxylase, and 17α-hydroxylase. This inhibition leads to decreased cortisol production, potentially leading to adrenal insufficiency.[4] Itraconazole can cause de-novo inhibition of adrenal steroidogenesis and produce a clinical syndrome of adrenal insufficiency but via the same mechanism also can precipitate an adrenal crisis in a patient having pre-existing borderline primary or secondary adrenal dysfunction.[5] Adrenal crisis is a life-threatening condition due to acute adrenal insufficiency characterized by hypotension and shock requiring immediate intravenous (IV) hydrocortisone and fluid resuscitation.

Secondary adrenal insufficiency can occur with disorders of pituitary gland, mainly tumors and inflammatory disorders. Acromegaly is a rare endocrine disorder characterized by excessive secretion of growth hormone (GH), usually due to a pituitary adenoma, leading to elevated levels of insulin-like growth factor 1 (IGF-1). This condition can result in various systemic complications, including metabolic disturbances, cardiovascular disease, and musculoskeletal abnormalities. In some cases of acromegaly, the disease becomes "burned out," with no detectable residual GH hypersecretion after an apoplexy causing destruction of tumor cells leaving

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an empty sella. Empty sella, a radiological finding where the sella turcica is partially or completely filled with cerebrospinal fluid, often associated with pituitary dysfunction including adrenocorticotropic hormone (ACTH) deficiency.[6]

Here we are describing a rare association of a burnt-out acromegaly with probably a subclinical secondary adrenal insufficiency becoming overt by use of itraconazole.

Case Report

A 67-year-old male with a history of diet-controlled type 2 diabetes and celiac disease initially presented to a primary health center with symptoms of a viral upper respiratory tract infection, including cough and fever lasting for 3 days. He was not on any chronic medications except for itraconazole 100 mg, prescribed by a dermatologist over the past 1 month for Tinea corporis. He was subsequently transferred to the emergency department due to severe fatigue, drowsiness, and inadequate oral intake. In the emergency department, the patient had a heart rate of 69 beats per minute, blood pressure of 96/60 mm Hg, oxygen saturation of 98% on room air, and a temperature of 36.7°C. Upon physical examination, the patient exhibited a reduced level of consciousness, with a Glasgow Coma Scale (GCS) score of 9/15.

Initial laboratory investigations (►**Table 1**) revealed elevated inflammatory markers. The electrolyte panel showed hyponatremia while potassium levels remained normal, and coagulation results were abnormal. The patient also had vitamin D insufficiency. Other tests, including renal and liver function tests, complete blood count, lipid profile, thyroid function tests, urine routine, urine culture, and chest X-ray, were all within normal ranges. The HbA1c was recorded as prediabetes. A random cortisol measurement was done in view of hyponatremia, yielding a low value.

Upon admission, the patient was started on IV fluids. With IV hydration, the GCS score improved slightly. The patient became more oriented and began opening his eyes spontaneously, eventually achieving a GCS score of 15/15.

Additionally, the short synacthen test was performed, showing an inadequate response (►**Table 1**). Consequently, adrenal insufficiency was diagnosed as the underlying cause of the hypotension and hyponatremia. The patient was treated initially with IV hydrocortisone and later switched to oral tablets. The patient was discharged on hydrocortisone tablets. Work-up etiology for adrenal insufficiency was not done at this point.

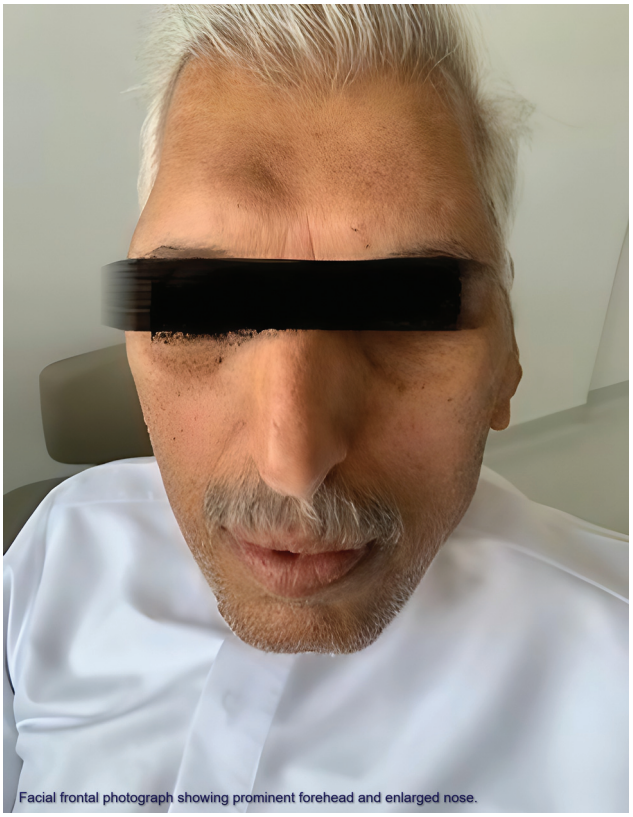

Fig. 1 Facial frontal photograph showing prominent forehead and enlarged nose.

Subsequently he was seen in an endocrinology clinic for follow-up. Acromegalic features were observed in the patient (►**Figs. 1** and **2**). On detailed questioning, the patient reported that he had developed acromegalic features around 30 years back. He was evaluated previously in his home country and was told to have normal IGF-1 level. He never had history suggestive of adrenal insufficiency in the past. He gives a history of decreased libido and erectile dysfunction for the last few years.

Table 1 Laboratory investigation done during admission

Component	Result	Reference range
C-Reactive protein (CRP)	56.1 mg/L	<5.0 mg/L
Procalcitonin (PCT)	0.31 ng/mL	<0.05 ng/mL
Sodium	120 mmol/L	136–145 mmol/L
Prothrombin time	13.7 seconds	9.7–11.8 seconds
HbA1C	5.9%	<5.7%
25 OH vitamin D total	39.4 ng/mL	30–100 ng/mL
Random cortisol level	210 nmol/L	>500 nmol/L
Post-ACTH stimulation cortisol (0.30 and 60 minutes)	147, 285, and 295 nmol/L	>500 nmol/L
ACTH	22 pg/mL	7.2–63.3 pg/mL

Fig. 2 Facial lateral photograph showing enlarged forehead, prominent nose, and prominent chin and jaw.

A comprehensive evaluation of pituitary hormone levels was requested, revealing hypopituitarism and hypogonadism. The laboratory results are shown in ►**Table 2**. A magnetic resonance imaging (MRI) scan was performed, revealing an empty sella **(►Fig. 3)** and retrospectively there was no history to suggest a pituitary apoplexy in the past. Consequently, a diagnosis of burnt-out acromegaly with an empty sella was made with respect to clinical phenotype, specifically skeletal features and presence of empty sella and biochemical hypopituitarism. In addition to hydrocortisone, the patient was also started on testosterone replacement.

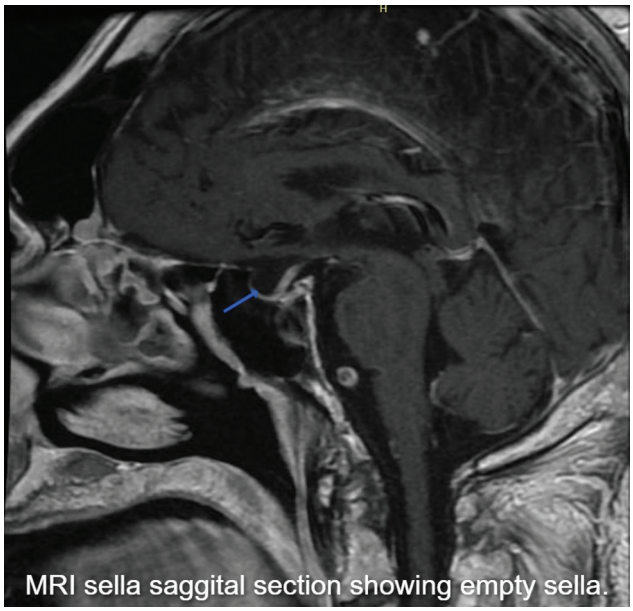

Fig. 3 MRI sella sagittal section showing empty sella. MRI, magnetic resonance imaging.

Discussion

Acromegaly is a rare endocrine disorder characterized by excessive GH secretion, typically due to a pituitary adenoma. This results in elevated levels of IGF-1. Without treatment, acromegaly sometimes can progress to a condition known as "burnt-out acromegaly," where GH and IGF-1 levels decrease, but acromegalic features persist especially skeletal features.[7] Imaging studies often reveal an empty sella, indicating significant atrophy of the pituitary gland.[7] In this case, the patient had acromegalic phenotype and exhibited low IGF-1 levels and an empty sella on MRI, consistent with burnt-out acromegaly. The introduction of itraconazole, an antifungal medication, is considered to have precipitated an adrenal crisis—a serious and potentially life-threatening condition.

In this patient with burnt-out acromegaly, there was underlying hypopituitarism which was not complete, hence the patient did not have any obvious symptom. This

Table 2 Laboratory investigation done during outpatient visit

Component	Result	Reference range
Insulin-like growth factor-1 (IGF-1)	11.5 ng/mL	54.7–185 ng/mL
Prolactin	40 mIU/L	86–324 mIU/L
Luteinizing hormone (LH)	1.5 mIU/mL	1.7–8.6 mIU/mL
Testosterone	0.4 nmol/L	6.68–25.7 nmol/L
Free androgen index	0.4%	24.3–72.1%
Sex hormone binding globulin (SHBG)	104 nmol/L	20.6–76.7 nmol/L
Free T4	15.3	12.0–22.0 pmol/L
TSH	1.380	0.27–4.2 uIU/mL

Abbreviation: TSH, thyroid-stimulating hormone.

mild secondary adrenal insufficiency with itraconazole treatment has led to clinical adrenal deficiency ending in an adrenal crisis.[5]

This case underscores the need for careful consideration of drug interactions in patients with chronic endocrine disorders and underscores the role of proper clinical examination in practice.

Conclusion

It is essential to assess adrenal function before starting itraconazole or similar medications in patients with known or suspected pituitary dysfunction. Baseline cortisol levels, ACTH stimulation tests, or other adrenal function tests may be warranted. If adrenal insufficiency is identified, appropriate corticosteroid replacement therapy should be initiated to prevent an adrenal crisis.

Financial Disclosure
None.

Patient Consent
The authors confirm that they have obtained written informed consent from the patient to publish the case and photos.

Ethical Approval
No prior ethical approval is required for single-case reports and small-case series, provided the patient or guardian provides informed consent.

Conflict of Interest
None.

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