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Combined Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State as the First Presentation of Acromegaly: Case Report and Literature Review

Shamma Alshamsi[1] Hour AlSheleh[2] Raya Almazrouei[1,3]

[1] Division of Endocrinology, Department of Internal Medicine, Tawam Hospital, Al Ain, United Arab Emirates
[2] Department of Internal Medicine, Tawam Hospital, Al Ain, United Arab Emirates
[3] Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

Address for correspondence Raya Almazrouei, MD, Division of Endocrinology, Department of Internal Medicine, Tawam Hospital, Al Ain, PO Box 15258, United Arab Emirates (e-mail: rmazrooei@seha.ae).

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Abstract

Acromegaly is characterized by excessive growth hormone secretion and is usually associated with glucose intolerance or diabetes mellitus. It is rare to be associated with life-threatening diabetes emergencies. Here, we present a case of a 38-year-old woman who initially presented with a severe hyperglycemia crisis that meets the criteria for both diabetes ketoacidosis and hyperosmolar hyperglycemic state. Subsequently, she was found to exhibit signs of typical acromegaly, including enlargement of hands, thick skin, and interdental spacing. The diagnosis was established based on typical clinical manifestations, hormonal assays, and radiological findings confirming pituitary macroadenoma. Timely identification and diagnosis are crucial for mitigating the potential complications associated with this condition.

Keywords
- diabetic ketoacidosis
- acromegaly
- hyperosmolar hyperglycemic state
- pituitary adenomas

Introduction

Acromegaly is characterized by excessive growth hormone (GH) secretion mostly from benign somatotroph pituitary adenomas. GH is normally secreted from the anterior pituitary gland in an episodic manner, mainly during sleep and exercise.[1] This secretion is controlled by negative feedback from circulating insulin-like growth factor 1 (IGF-1).[2] However, in acromegaly, this feedback is lost, leading to chronic GH elevation from pituitary adenomas.[3] These adenomas are mostly sporadic but can be familial as well.[4,5] Clinically, acromegaly results in coarse facial features, acral enlargement, and organomegaly. One of the complications of GH excess is insulin resistance, which can lead to diabetes mellitus (DM).[5] Although rare, acromegaly can present with diabetic ketoacidosis (DKA), which necessitates medical attention.[6] In this report, we describe a young lady who presented with altered mental status and was found to have severe hyperglycemia. Laboratory findings confirmed a combined presentation of DKA and hyperosmolar hyperglycemic state syndrome (DKA-HHS). Further investigations led to the diagnosis of acromegaly. This case highlights the importance of very careful clinical assessment and thorough history taking, especially in situations where changes, such as those seen in acromegaly, may be subtle or not easily recognizable due to ethnic variations.[7] It underscores the need for heightened clinical suspicion of the diagnosis of rare presentations like the combined DKA-HHS syndrome associated with acromegaly.

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Case Description

A 38-year-old Ethiopian lady presented to the emergency room (ER) with altered mental status, generalized weakness, headache, and dizziness. The clinical history was limited because of the patient's mental status. The rest of the systemic review was unremarkable at that point. She had no significant past medical history and was not on regular medications.

On physical examination, she was hemodynamically stable with a temperature of 37.4°C, pulse rate of 94 beats/minute, and blood pressure of 124/67 mm Hg, but subsequently exhibited persistent high blood pressure readings of 142 to 165 mm Hg systolic and 91 to 98 mm Hg diastolic. The patient was arousable with a Glasgow Coma Scale of 13, disoriented, and dysarthric. Thorough examination was not performed at this point.

Initial investigations (►**Table 1**) showed hyperglycemia with blood glucose of 33 mmol/L (3.9–7.8), acidosis with pH of 7.23 (7.35–7.45), and positive point-of-care ketones above >7 mmol/L (0.1–0.6). Further laboratory findings confirmed DKA with overlapping HHS (blood glucose of more than 600 mg/dL, plasma effective osmolality of more than 320

Table 1 Laboratory results

Initial blood results	Results	Reference
Blood glucose (mmol/L)	33	3.9–7.8
Serum osmolality (mOsm/kg)	350	285–295
Arterial pH	7.23	7.35–7.45
Bicarbonate (mmol/L)	8	22–29
Beta-ketones (mmol/L)	>7	0.1–0.6
Anion gap	37	7–16
Serum sodium (mmol/L)	138	136–145
Serum potassium (mmol/L)	5.4	3.2–5.5
Creatinine (micromole/L)	155	44–80
Urea (mmol/L)	11.7	2.80–8.10
eGFR (mL/min)	36	≥60
WBC ($\times 10^9$/L)	7.6	4.1–10
C-Reactive protein (mg /L)	41.3	≤5.0
HbA1C%	16.4%	4.3–5.6%
GAD antibodies (IU/mL)	2	≤17
Anti IA-2 antibodies (IU/mL)	<3	≤28
Further investigations		
IGF-1 (nmol/L)	60.7	12.17–29.81
Growth hormone (milli IU/L)	39.4	0–26
ACTH (pmol/L)	3	1.6–13.9
Cortisol (nmol/L)	431	64–536
TSH (milli IU/L)	0.154	0.40–4.20
Free T4 (pmol/L)	8.5	12–22 pmol/L
Prolactin (pmol/L)	45.8	102–496
LH (milli IU/L)	0.6	Follicular phase 2.4–12.6 Ovulation phase 14.0–95.6 Luteal phase 1.0–11.4 Postmenopausal 7.7–58.5
FSH (milli IU/L)	1.8	Follicular phase 3.5–12.5 Ovulation phase 4.7–21.5 Luteal phase 1.7–7.7 Postmenopausal 25.8–134.8
Estradiol (pmol/L)	45.5	Follicular phase 45.4–854 Ovulation phase 115–1,461 Luteal phase 82–1,251 Postmenopausal <18.4–505

Abbreviations: ACTH, adrenocorticotropic hormone; eGFR, estimated glomerular filtration rate; FSH, follicle-stimulating hormone; GAD, glutamic acid decarboxylase; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; WBC, white blood cell.

mOsmo/L) and acute kidney injury. HbA1c was elevated at 16.4 (4.3–5.6)% and autoimmune antibodies revealed negative glutamic acid decarboxylase antibodies and anti-islet antigen 2. While in the ER, the patient underwent head computed tomography for the altered mental status, which revealed presence of suprasellar lesion for which dedicated pituitary magnetic resonance imaging (MRI) was performed later.

Aggressive hydration and intravenous insulin were initiated as per DKA treatment protocol and the patient was admitted to the intensive care unit. During the acute phase of management, the patient required 88 units of insulin infusion over the first 24 hours. Her insulin requirement then ranged from 28 units to 48 units per day over subsequent days.

Once the patient was out of DKA and recovered neurologically, further history and detailed examinations were attempted when she was on the floor. The patient denied typical symptoms of headache, visual changes, excessive sweating, or joint pain. She reported regular menstrual cycles which appeared inconsistent with her biochemical profile (mentioned below) that was showing hypogonadotropic hypogonadism. This discrepancy might be attributed to overall denial of the patient to the diagnosis and treatment. Notably, she also reported spontaneous pregnancies.

Detailed examination revealed notable phenotypical features of acromegaly with interdental spacing, thickened skin, enlarged hands, acanthosis nigricans, and skin tags on the neck.

Diagnosis of acromegaly was confirmed with further investigations (►**Table 1**) confirming elevated IGF-1 and random GH. The rest of the pituitary profile showed central hypothyroidism, hypogonadotropic hypogonadism, and low prolactin level. Pituitary MRI showed a minimally extending suprasellar mass involving the cavernous sinus bilaterally with superior displacement of the optic chiasm (►**Fig. 1**).

Following an uncomplicated hospital course, the patient was discharged on day 7 on 48 units of insulin (Mixtard Insulin 30/70 twice daily), metformin 1 g twice daily, amlodipine 5 mg daily, and levothyroxine 50 mcg daily. Follow-up appointments were arranged with the ophthalmology clinic for visual field testing and with the neurosurgery clinic to discuss transsphenoidal surgery. Unfortunately, the patient declined surgery and lost to follow-up.

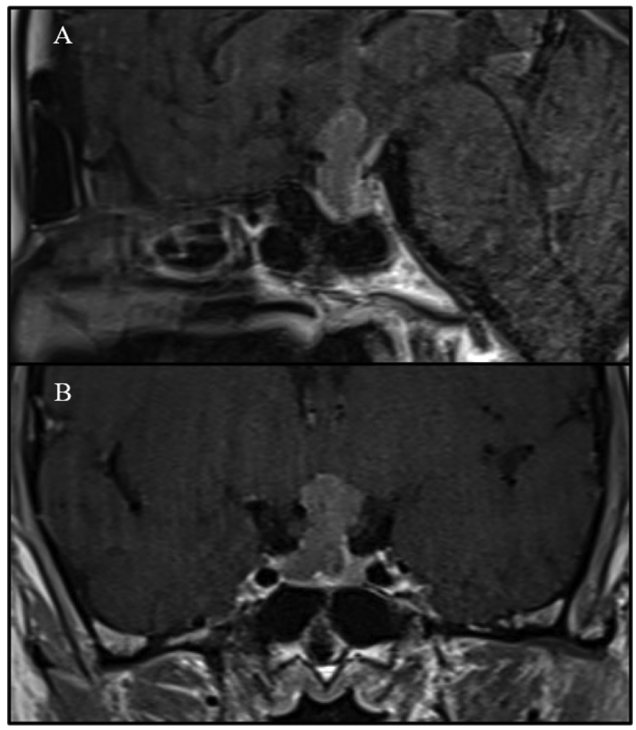

Fig. 1 Magnetic resonance imaging with sagittal (**A**) and coronal (**B**) sections. It revealed a sizable sellar and suprasellar mass measuring $22 \times 12 \times 9$ mm, consistent with a pituitary macroadenoma. It minimally extends into the cavernous sinuses (Knosp grade 1) without encasing the internal carotid artery, displaces the optic chiasm superiorly, and slightly deviates the pituitary stalk to the left.

Discussion

This case highlights a rare and severe initial presentation of acromegaly with diabetes emergency, a combination that is unusual and poses significant diagnostic challenge. The patient presented with altered mental status, generalized weakness, and hyperglycemia severe enough to meet the criteria for both DKA and HHS.

Glucose intolerance and overt diabetes are common in acromegaly, with studies suggesting a prevalence of 30 to 50% among patients.[8] Progression to DKA, however, is rare and usually occurs in the context of severe insulin resistance exacerbated by additional stressors such as infection or inadequate insulin therapy. DKA in acromegaly is often a marker of long-standing, undiagnosed disease where GH levels have been elevated for a prolonged period, leading to significant metabolic derangements.

The interplay between hyperglycemia, GH, and IGF-1 is complex, particularly in the context of acromegaly. In individuals without acromegaly, hyperglycemia typically suppresses GH secretion through somatostatin release. However, in acromegaly, GH secretion remains autonomous and resistant to this suppression leading to persistently elevated GH levels. While chronic hyperglycemia and insulin resistance generally impaired hepatic IGF-1 production, in acromegaly, the excessive GH drives IGF-1 production, overriding these effects. This dysregulation exacerbates the severe metabolic disturbances characteristics of acromegaly, including hyperglycemia, insulin resistance, and associated complications. Although IGF-1 levels may be lower than expected due to hyperglycemia-induced impairment in hepatic production, they remain elevated overall due to the persistent GH hypersecretion.[9]

In acromegaly, the excess production of GH leads to significant metabolic disturbances. GH directly impairs insulin signaling, contributing to insulin resistance, particularly in the liver and skeletal muscle.[8] GH-induced insulin resistance is primarily associated with increased lipolysis, where free fatty acids (FFAs) are released into the bloodstream. FFAs inhibit insulin-stimulated glucose uptake in skeletal muscle, leading to hyperglycemia.[8] Pharmacological inhibition of lipolysis could restore insulin sensitivity during

GH exposure, emphasizing the critical role of FFAs in this process.

Experimental studies have shown that GH not only stimulates lipolysis but also affects glucose metabolism and uptake by inhibiting insulin signaling directly at the tissue level, particularly in muscle and adipose tissues, further exacerbating insulin resistance.[10]

The substrate competition between FFAs and glucose further contributes to the metabolic disturbances seen in acromegaly. This competition occurs at the tricarboxylic acid cycle entry point, where the presence of FFAs inhibits glucose oxidation, worsening hyperglycemia.[11]

Despite the elevated levels of IGF-1 in acromegaly, which normally has insulin-like effects, it fails to counteract the insulin-antagonistic actions of GH.[8] IGF-1's cross-reactivity with insulin receptors in skeletal muscle does not sufficiently improve glucose uptake, leaving the hyperglycemia unresolved.[12] This inability of IGF-1 to mitigate GH's effects highlights the dominant role of GH in driving insulin resistance in acromegaly.[8]

Chronic exposure to elevated GH levels leads to β-cell dysfunction in the pancreas, similar to what is seen in type 2 DM. This dysfunction may be due to lipotoxicity caused by increased FFAs, leading to impaired insulin secretion and further contributing to hyperglycemia and diabetes in acromegaly.[8]

GH-induced lipolysis not only raises FFA levels but also promotes hepatic ketogenesis, which can lead to DKA when combined with the insulin-resistant state.[8] The excess FFAs are converted into ketone bodies in the liver, which, in the presence of relative insulin deficiency, can precipitate DKA, particularly under conditions of metabolic stress.[11]

Previous case reports have documented instances where DKA was the initial presentation of acromegaly. These cases often involve middle-aged individuals, predominantly in their 30s to 50s, similar to the patient in this report. Commonalities include the absence of classical acromegaly symptoms before the acute metabolic crisis, which complicates early diagnosis. However, upon recovery from DKA, patients often exhibit subtle signs of GH excess, such as coarse facial features, enlarged hands and feet, or skin tags.

Diagnosing acromegaly in the context of an acute metabolic crisis like DKA is particularly challenging. The suprasellar mass identified on imaging, combined with the clinical features observed post-recovery, was crucial in diagnosing acromegaly in our patient. The biochemical confirmation of elevated IGF-1 and GH levels solidified the diagnosis.

The initial management focused on stabilizing the acute metabolic derangements and once stabilized, the focus to be shifted to managing the underlying acromegaly and its complications. It is well documented that glycemic control tends to improve significantly following definitive treatment of acromegaly with trans-sphenoidal surgery, as GH and IGF-1 levels normalize. This improvement is attributed to the resolution of severe insulin resistance, reduced hepatic glucose production, and enhanced peripheral glucose uptake. Consequently, insulin requirements typically decrease, as observed in similar cases reported in the literature.[12]

Conclusion

This case highlights the need for heightened awareness of acromegaly as a potential underlying cause of unexplained DKA. Clinicians should be particularly vigilant when patients present with DKA without obvious precipitating factors, and where clinical features such as coarse facial features, enlarged hands/feet, or other signs of GH excess are noted. Early recognition and intervention are critical in preventing long-term complications associated with untreated acromegaly, such as cardiovascular disease, diabetes-related complications, and increased mortality.

Patient Consent Statement

Verbal informed consent was obtained from the patient for publication of this case report.

Authors' Contributions

All authors were involved in data collection, manuscript drafting, and finalizing. S.H. and H.A. collected the data. S.H. and R.A. were involved in intellectual input and performed manuscript writing, editing, and review. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Compliance with Ethical Principles

No ethical approval is required for single case report.

Availability of Data and Material

For confidentiality reasons, the original data cannot be shared.

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Conflict of Interest

None declared.

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