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Case Report

Insulin Requirements in Untreated Acromegaly: From 200 to 0

Michael B. Goldstein,[1] Lauren Bellavia,[2] Tiffany Kurian,[2] and Stanislaw Klek[1]

[1]Division of Endocrinology, NYU Long Island School of Medicine, Mineola, NY 11501, USA
[2]Department of Medicine, NYU Long Island School of Medicine, Mineola, NY 11501, USA

Correspondence: Stanislaw Klek, MD, NYU Langone Diabetes & Endocrinology, 101 Mineola Boulevard, 2nd Floor, Mineola, NY, USA, 11501.
Email: stanislaw.klek@nyulangone.org.

Abstract

We describe a patient with acromegaly presenting in diabetic ketoacidosis who was able to achieve euglycemia despite discontinuation of all antihyperglycemic therapy prior to surgical or medical treatment for his acromegaly. No previous cases of acromegaly presenting in diabetic ketoacidosis have reported glycemic normalization without antihyperglycemic therapy prior to acromegaly treatment. Our case highlights this unique outcome and postulates that pancreatic β-cell resiliency may be influential on insulin resistance since our patient achieved euglycemia despite a persistent state of excess growth hormone and insulin-like growth factor-1. Our case further emphasizes that consideration for acromegaly should be given in patients presenting with severe insulin resistance and pertinent medical history and physical examination features, and it emphasizes the dramatic range of insulin requirements in patients with acromegaly.

Key Words: acromegaly, diabetic ketoacidosis, insulin-like growth factor-1, colon cancer

Abbreviations: DKA, diabetic ketoacidosis; GH, growth hormone; IGF-1, insulin-like growth factor 1; IR, insulin resistance; IV, intravenous..

Acromegaly is a clinical disorder that occurs due to excess production of growth hormone (GH), most commonly from a pituitary adenoma. It has a reported prevalence of 34 to 137 cases per million [1], with manifestations arising directly from the effects of GH as well as indirectly from GH-induced secretion of hepatic insulin-like growth factor-1 (IGF-1). Acromegaly is associated with significant metabolic effects, the hallmark of which is insulin resistance (IR), as excess GH and IGF-1 disrupt hormone homeostasis and lead to hyperglycemia and both hepatic and peripheral IR [1]. Approximately 50% of patients develop impaired glucose tolerance, with overt diabetes in up to 35% of cases [2].

Diabetic ketoacidosis (DKA) can be a late complication of acromegaly, occurring as an initial manifestation of disease in 1% of cases [3] and portending glycemic management with insulin therapy until undergoing treatment for acromegaly [4]. Furthermore, acromegaly is associated with numerous somatic effects, with development of colonic carcinoma as one particularly devastating consequence that occurs in 4% to 10% of patients [5]. Excess GH and IGF-1 promote unregulated cellular growth in colonic epithelium, which can lead to malignant neoplastic changes [6]. We present a case of acromegaly in a patient with a remote history of colon cancer, presenting as DKA with severe IR that evolved to euglycemia despite discontinuation of all antihyperglycemic therapy and having not yet undergone treatment for acromegaly.

Case Presentation

A 32-year-old man presented to the emergency department with generalized weakness, epigastric pain, nausea, and vomiting of 3 days duration. He reported a medical history of colon cancer with an associated colovesicular fistula that was diagnosed 7 years prior during evaluation of abdominal pain, constipation, and hematuria without any family history of colonic malignancy, which had been subsequently treated with colectomy and chemoradiation. He denied taking any medications on a regular basis. On presentation, he was noted to be tachycardic and tachypneic, with initial physical exam only notable for dry mucus membranes. His height was 185.4 cm, weight was 92.6 kg, and body mass index was 26.93 kg/m^2. A random serum glucose was > 1000 mg/dL (> 55.5 mmol/L) (reference range, 70-100 mg/dL; 3.89-5.55 mmol/L). Venous blood gas was consistent with metabolic acidosis, with a pH of 7.19 (reference range, 7.3-7.4) and bicarbonate of 9.2 mEq/L (9.2 mmol/L) (reference range, 21-28 mEq/L; 21-28 mmol/L). He had marked ketonuria on urinalysis and a serum β-hydroxybutyrate of 12.9 mmol/L (134.2 mg/dL) (reference range, < 0.3 mmol/L < 3.1 mg/dL). He was diagnosed with DKA and admitted to the Medical Intensive Care Unit for initiation of intravenous (IV) insulin infusion. His hemoglobin A1c was 11.6% (103 mmol/mol) (reference range, < 5.7% < 39 mmol/mol), confirming the new diagnosis of diabetes. The C-peptide level was 1.4 ng/mL (0.5 mmol/L) (reference range, 0.5-3.3 ng/mL; 0.2-1.1 mmol/L) and anti-glutamic acid decarboxylase and anti-zinc transporter

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8 antibodies were negative. He was initially treated using our institution-based DKA protocol of continuous IV regular insulin, with very high infusion rates totaling > 200 units daily. Once DKA resolved, he was transitioned to a subcutaneous insulin regimen and ultimately required 60 Units of basal insulin subcutaneously every 12 hours with 30 Units of prandial insulin 3 times daily before meals to maintain euglycemia.

Diagnostic Assessment

Given these high insulin requirements, he was evaluated for underlying etiologies of his IR. Evaluation for precipitating factors of DKA, including thorough infectious workup and dietary review, was unrevealing. His severe IR, in consideration with a unique medical history of colon cancer at a young age, prompted clinical suspicion for acromegaly. The patient was re-interviewed in this context and endorsed increased shoe size in his mid-twenties, as well as requiring re-fitting of his bowling ball over the past year due to increased finger size. On re-examination, he was noted to have frontal bossing, macrognathia, macroglossia, and prognathism; features that were previously subtle without appropriate clinical context [Fig. 1].

Diagnostic evaluation for acromegaly was initiated. His IGF-1 was elevated at 1036 ng/mL (135.4 nmol/L) (reference range, 82-242 ng/mL; 10.7-31.6 mmol/L) with a concomitant glucose value of 324 mg/dL (18 mmol/L). Magnetic resonance imaging of the brain revealed a hypo-enhancing 1.3-cm lesion enlarging the left lateral pituitary gland [Fig. 2]. He was subsequently diagnosed with acromegaly secondary to a pituitary macroadenoma. Further hormonal testing revealed adrenocorticotrophic hormone, follicle-stimulating hormone, luteinizing hormone, and thyroid stimulating hormone all within reference range, with prolactin elevated at 103.4 ng/mL (103.4 µg/L) (reference range, 3.5-19 ng/mL; 3.5-19 µg/L), suspected to be due to stalk effect.

Figure 1. Our patient on re-examination, with noted frontal bossing, macrognathia, macroglossia, and prognathism.

Treatment

He was referred to ophthalmology for formal visual field testing and to neurosurgery for resection and was discharged on an insulin regimen of 60 units of glargine twice daily and 30 units of lispro prior to each meal.

Outcome and Follow-Up

Approximately 3 months after diagnosis, he was evaluated by neurosurgery but had not yet undergone surgical resection or medical management for his acromegaly. He did, however, report significant improvement in his blood sugar within 2 weeks of discharge, which prompted self-de-escalation and then discontinuation of his insulin regimen. He was continued on a single oral antihyperglycemic agent, metformin, with self-cessation only 2 weeks later due to achievement of euglycemia. A repeat hemoglobin A1c at his 3-month follow-up visit was 6.1% (43 mmol/mol), with repeat IGF-1 of 1602 ng/mL (209.4 nmol/L), indicating glycemic improvement.

Discussion

The metabolic effects that occur in patients with acromegaly are facilitated through GH and IGF-1. GH stimulates gluconeogenesis, glycogenolysis, and lipolysis, and downregulates peripheral glucose uptake receptors, ultimately promoting glucose intolerance. IGF-1, conversely, has insulin-agonistic properties by enhancing insulin sensitivity. In patients with acromegaly, however, the hyperinsulinemia fails to compensate against the excess GH, resulting in IR [1, 2].

Studies are inconsistent in showing associations between GH/IGF-1 and the development of IR in acromegaly. Fukuoka et al demonstrated no significant correlation but cited the ratio of GH/IGF-1 in glucose intolerance, with a low ratio associated with IR [7], while Puder et al demonstrated that high IGF-1 is associated with lower insulin sensitivity and may be more predictive than GH [8]. The mechanism of IR in acromegaly may additionally be explained by pancreatic β-cells, as increased insulin production from β-cells attempts to counterbalance IR with eventual insulin deficiency resulting [1,2]. Kasayama et al found that euglycemic patients with acromegaly can compensate via this mechanism, whereas hyperglycemic patients with acromegaly cannot, thus indicting impaired β-cell function as the determinant of glucose intolerance [9]. Glucose impairments associated with acromegaly are typically reversed after treatment of the underlying disorder. With both pituitary surgery and/or hormone-antagonist therapy, biochemical parameters normalize, β-cell function improves, and IR decreases [2, 9].

Moreover, several studies have shown that patients with acromegaly are at an increased risk of development of benign and malignant colonic neoplasia [6]. It has been reported that GH and IGF-1 are involved in the promotion of cellular proliferation of colonic epithelium by activating signal transduction pathways necessary for cellular growth [5, 6]. Additionally, GH and IGF-1 are thought to have a component of anti-apoptotic activity when in excess, specifically in the colonic mucosa. Combined, these pro-mitotic and anti-apoptotic properties of GH and IGF-1 on colonic epithelium promote unregulated division, which is purported to be involved in the malignant transformation of the mucosa [5].

To our knowledge, we present the first case of a patient with acromegaly presenting in DKA with insulin requirements

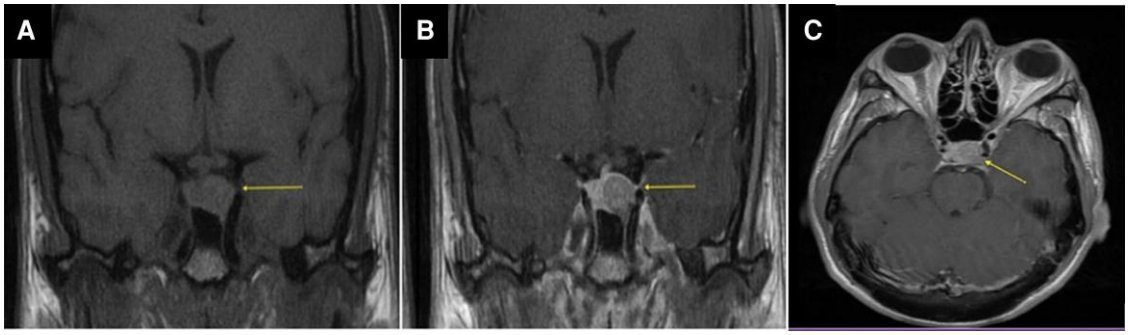

Figure 2. MRI brain findings: coronal T1-weighted pre-contrast (A) and post-contrast (B) images through the pituitary gland demonstrating a hypo-enhancing 1.3-cm left lateral suprasellar mass (arrows), consistent with a pituitary macroadenoma. Axial T1-weighted post-contrast image (C) again demonstrates findings consistent with a pituitary macroadenoma (arrow).

> 200 Units per day who was able to achieve improved glycemia despite discontinuation of all antihyperglycemic therapy prior to surgical, or even medical, treatment for acromegaly. While there have been similar outcomes of drug-free remission reported in the context of type 2 diabetes mellitus [10], there are no reports of patients with acromegaly who presented in DKA who were able to discontinue insulin and/or oral or injectable anti-hyperglycemic therapy due to improved glycemia without having undergone intervention for acromegaly [4]. Our results support the concept that excess GH and IGF-1 may not be as contributory to development of IR in acromegaly as previously thought. We postulate that pancreatic β-cell resiliency may be more influential on IR, since our patient achieved improved glycemia despite a persistent state of excess GH and IGF-1. While exogenous insulin allowed β-cell function to recover and thus led to glycemic improvement, the continued effect of persistent GH excess on glucose homeostasis remains to be seen. Additionally, to our knowledge, we present the first case of acromegaly presenting as DKA in a patient with a pertinent history of colon cancer, which was pivotal in invoking clinical suspicion for underlying causes of insulin resistance [4].

Learning Points

- Pancreatic β-cell resiliency may be more influential on insulin resistance than GH/IGF-1
- Insulin resistance leads to compensatory hyperfunction of β-cells to maintain euglycemia, which can ultimately lead to β-cell failure (glucotoxicity)—exogenous insulin enables the β-cells to recover function
- Acrofacial features of acromegaly have an insidious onset and slow progression and therefore may remain unnoticed in routine clinical care
- Acromegaly should be considered in patients presenting with severe insulin resistance and pertinent medical history and physical exam features

Author Contributions

All authors made individual contributions to authorship. M.G. and S.K. were involved in the diagnosis and management of this patient and manuscript submission. M.G., L.B., and T.K. were involved in manuscript compilation. All authors reviewed and approved the final draft.

Disclosures

The authors have nothing to disclose.

Data Availability

Original data generated and analyzed during this study are included in this published article.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

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