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Diabetic Ketoacidosis in Undiagnosed Acromegaly: A Case Report and Literature Review

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INTRODUCTION

Diabetic ketoacidosis (DKA) is both a potentially deadly hyperglycemic crisis and one of the most common causes of diabetes-related hospitalization in the U.S.[1,2] DKA currently is not established as a complication of acromegaly,[3-5] even though many authors have described their association.[6,7] This case reports a middle-aged male patient with a long history of untreated acromegaly who developed DKA.

Acromegaly is a rare endocrinologic disease first mentioned in 1886 by Perrier Marie, characterized by overproduction of growth hormone (GH), and in most cases from a pituitary adenoma.[8,9] It often is diagnosed between 40 and 50 years old,[10] and the common manifestations are acral growth, facial features deformities, soft tissue edema, hyperhidrosis, visual impairment, menstrual disturbances in women, and decreased libido in men.[11,12]

Diabetes mellitus (DM) is a common complication of acromegaly, with a prevalence ranging from 19 - 56%.[3,13] The primary mechanism of DM in acromegaly is growth hormone (GH)-induced insulin resistance,[14] thus hyperosmolar hyperglycemic state (HHS) would be expected as in Type 2 DM complications, instead of DKA.[15]

CASE REPORT

A 41-year-old male presented with a two-week history of polyuria, polydipsia, blurred vision, and dizziness, which progressed to nausea and vomiting for the prior two days. He had a medical history of hypertension, and a family history of Type 2 diabetes mellitus in his mother.

Physical examination was remarkable for a body mass index of 30 kg/m^2, blood pressure of 92/50 mmHg, heart rate of 105 beats/min, dry mucous membranes, a fruity odor to his breath, and physical findings suggestive of acromegaly: coarse facial features, enlarged mandible, enlarged-fleshy nose, increased space between the lower incisors, and bony overgrowth of the hands (Figure 1).

Visual field examination was unremarkable. Initial blood workup showed high anion gap metabolic acidosis (pH 7.27, bicarbonate 13.2mEq/L, and anion gap of 25mEq/L), serum glucose 472 mg/dl, glycosylated hemoglobin (HbA1c) 15.2%, ketones present in blood and urine, and serum osmolality 298 mOsm/kg.

Current 2021 British DKA guidelines for treatment,[16] as well as ADA 2009 latest guidelines for hyperglycemic crisis in adults,[17] recommended that the initial therapy starts with 0.9% sodium chloride solution and regular insulin infusion should be initiated at a rate of 0.1 units/kg/h. Efforts also should be made to maintain potassium in normal range. Hourly reassessments are needed to maintain blood glucose below 200 mg/dL until DKA resolves. This patient responded avidly to therapy and rapidly stabilized with expected ranges of blood glucose, pH, and bicarbonate.

Magnetic resonance imaging (MRI) of the head revealed a sella turcica mass (0.82 x 0.59 inches) with bilateral cavernous sinus invasion and likely mass effect on the optic chiasm (Figure 2).

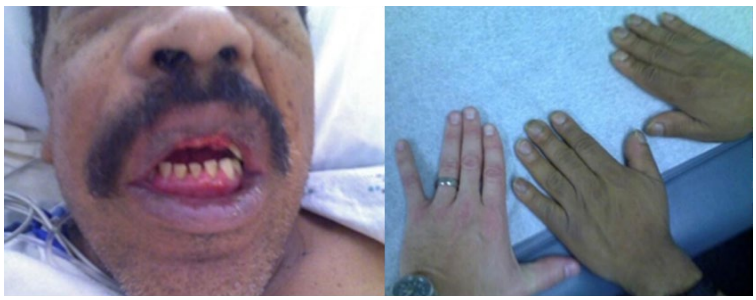

Figure 1. Patient shows coarse facial features, enlarged mandible, enlarged-fleshy nose, increased space between the lower incisors (left image), and bony overgrowth of the hands (right image).

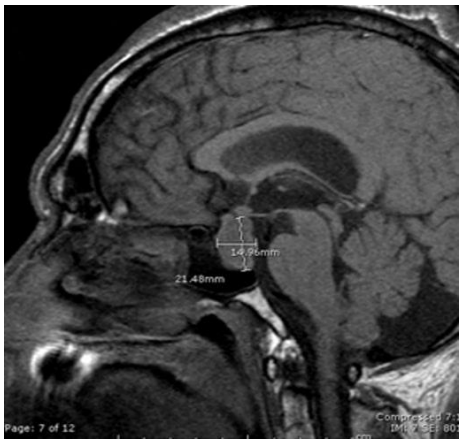

Figure 2. MRI showed a homogeneously enhancing hypointense T1/isointense T2 mass arising from the sella turcica.

An acromegaly laboratory panel confirmed the disease; random GH level was 98.2 ng/ml (normal 0-6 ng/ml) and insulin-like growth factor-1 (IGF-1) was 398 ng/ml (normal 101-267 ng/ml). Additional pituitary hormonal testing was unremarkable. A fasting C-peptide was 1.1 ng/dl (1.1-5 ng/dl), indicating some degree of insulin secretory reserve. Glutamic acid decarboxylase (GAD65) antibodies were negative, ruling out autoimmunity-related diabetes.

The patient underwent trans-nasal, trans-sphenoidal resection of the pituitary mass without complications, and biopsy confirmed pituitary adenoma (Figure 3).

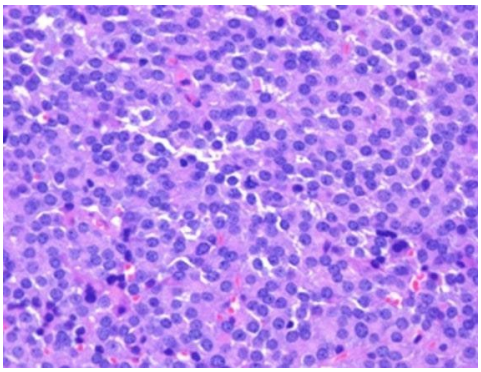

Figure 3. Pituitary adenoma composed of uniform, monomorphic polygonal cells arrayed in cords, with evidence of modest mitotic activity (400X).

Discharged treatment included subcutaneous insulin and metformin. At two-week follow-up, his coarse facial features slightly improved (Figure 4). At two months, the IGF-1 remained elevated at 837 ng/ml (98-261), indicating residual tumor. The patient was scheduled for a second MRI of the sella and consultation for stereotactic radiation therapy. Unfortunately, the patient was lost to follow-up.

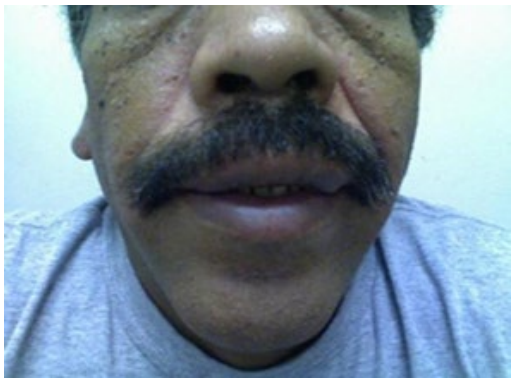

Figure 4. Improvement of coarse facial features two weeks post-surgery.

DISCUSSION

The DKA episode was the initial presentation of the acromegaly in this patient. It was likely due to a combination of severe insulin resistance from acromegaly and impaired insulin secretion (or relative insulin deficiency) from chronic undiagnosed hyperglycemia. Although there are a few reports of DKA as a complication of acromegaly,[6,7] the association was not well established.

Diabetes mellitus is a common complication of GH excess and caused by hepatic and peripheral insulin resistance.[18] At the hepatic level, GH increases gluconeogenesis and glycogenolysis. Peripherally, GH inhibits glycogen synthesis and glucose oxidation.[19] Growth hormone excess also causes increased lipolysis and, as a consequence, an increase in free fatty acid, which may contribute to insulin resistance.[20]

Diabetic ketoacidosis occurs in the presence of insulin deficiency and excess of counterregulatory hormones like GH.[7] The diabetogenic effect of GH initially is compensated by hyperinsulinemia;[21] if GH excess remains, fasting hyperglycemia may develop, often corresponding with a fall in fasting insulin levels. Finally, the insulin response to carbohydrate exposure is decreased,[14] which could result in DKA.[6,7]

Islet cells may undergo progressive changes when exposed to prolonged high levels of GH, which could result in cell degeneration, a reduction in insulin production, and finally DKA.[22] However, this mechanism has been borne out only in animal studies. An autopsy from an acromegalic woman who became diabetic and required insulin showed larger and more abundant islets with hypergranular beta cells,[23] suggesting the initial hyperglycemic state with normal insulin secretion.

Another plausible explanation was that acromegalic patients who develop DKA might have DM independent of their acromegaly.[24] Two important risk factors for DM secondary to acromegaly are hypertension and a positive family history of DM.[13] Both were present in our patient. In these patients, chronic glucose toxicity leads to insulin resistance and contributes to impairment of insulin secretion.[25]

Our patient had characteristics of ketosis prone, antibody-negative diabetes mellitus according to the A β classification system,[26] in which it was hypothesized that chronic hyperglycemia increases susceptibility of the beta cell to desensitization and alters post-insulin receptor signaling.[27]

Endocrine remission occurs in 50% of GH-secreting macroadenomas after surgery.[14] Remission was not seen in this patient, owing to the presence of an unresected tumor in his cavernous sinuses. During follow-up, the IGF-1 level remained elevated, reflecting the presence of residual tumor. In previous case reports of DKA in acromegalic patients, complete discontinuation of insulin therapy was possible after GH level normalization.[7,24,28] In our patient, the clinical scenario indicated that insulin discontinuation would not be possible, presumably due to persistent GH-induced insulin resistance that could yield another DKA episode.

If the patient was not lost to follow-up, further treatment or cure of his acromegaly would have revealed the extent to which his hyperglycemia and DKA were the result of acromegaly.

LIMITATIONS

Our patient had the phenotype for Type 2 DM, with obesity, age greater than 30 years, and a positive family history. This may have led to an atypical presentation of Type 2 DM rather than acromegaly-related DKA.

CONCLUSIONS

Growth hormone excess in acromegaly antagonizes insulin action both at the hepatic level and peripherally, making DKA an unlikely complication. It might be caused by B-cell failure due to chronic hyperglycemia. DKA can be managed with positive results, as well as hyperglycemic state after DKA control, until remission of the secreting-GH pituitary adenoma. This case report suggested that DKA was a possible complication of acromegaly and that it should be recognized as one.

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