Acromegaly Presenting as Diabetic Ketoacidosis: Thinking Beyond Diabetes Mellitus

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Introduction

Acromegaly is an acquired disorder caused by excessive production of GH and IGF-1 and characterized by somatic disfiguration and systemic manifestations.[1] It is due to monoclonal growth hormone producing pituitary adenoma in 90% of cases. Acromegaly is rare, with an incidence of three cases per million persons per year.[2] Due to its insidious onset and slow progression the diagnosis of acromegaly typically is delayed 4-10 years after symptom onset (mean age at diagnosis 40 years).[1]

Acromegaly affects men and women equally.[1] Impaired glucose tolerance and diabetes mellitus (DM) are common in patients with acromegaly, with a prevalence of 36% and 30%, respectively.[2] Diabetic ketoacidosis (DKA) is a rare complication of acromegaly with only a few cases reported in the English medical literature.[3-15] Factors that promote ketoacidosis in acromegalic patients include infection, surgical procedures, cessation of octreotide therapy, and excessive ingestion of sugar-containing soft drinks.[7]

We present a case of a patient with no past medical history of DM who presented to the hospital for DKA and was found to have acromegaly.

Case Report

A 41-year-old Hispanic female presented with a three-month history of weakness. She also complained of a seven-day worsening of polydipsia and polyuria. Her prior medical history was significant for hypertension and hyperlipidemia. Her family history was noteworthy for type 2 DM in her mother. The patient noticed an increase in the size of her hands and feet for approximately 12 years, with an increase in shoe size from 7.5 to 9. Menstrual periods had been absent for approximately six years.

The physical examination was remarkable for a body mass index of 39 kg/m^2, blood pressure of 138/80 mmHg, heart rate of 98 beats/min, coarse facial features, and enlarged hands. Initial laboratory studies revealed a glucose of 359 mg/dl, bicarbonate of 8.4 mmol/L, ketones present in blood and urine, and an anion gap of 24. Arterial blood gas revealed pH at 7.27 with a pCO2 of 18 mmHg. Glycosylated hemoglobin (HbA1c) was 11.7 percent. There was neither laboratory nor physical evidence of infection, ischemia, or illicit drug use.

A random growth hormone (GH) level was elevated at 98.2 ng/ml (0-6) and insulin-like growth factor-1 (IGF-1) was elevated at 398 ng/ml (101-267), consistent with acromegaly. Other laboratory test results are included in Table 1.

Magnetic resonance imaging of the pituitary sella showed a mass arising from the pituitary that measured 2.1 x 1.8 cm, with bilateral cavernous sinus invasion and mass effect on the optic chiasm (Figure 1).

Table 1. Other laboratory values obtained on patient.

Laboratory Test	Value	Normal range
Thyroid-stimulating hormone (TSH)	0.32 μIU/ml	0.34 - 4.82
Free thyroxine	1.4 ng/dl	0.9 - 1.8
Morning adrenocorticotropic hormone	37.6 pg/ml	7.2 - 63.3
Morning cortisol	18.9 mcg/dl	4.3 - 22.4
Luteinizing hormone	0.2 mIU/ml	1.5 - 9.3
Follicle-stimulating hormone	2.7 mIU/ml	1.4 - 18.1
Prolactin	30 ng/ml	4.8 - 23.3

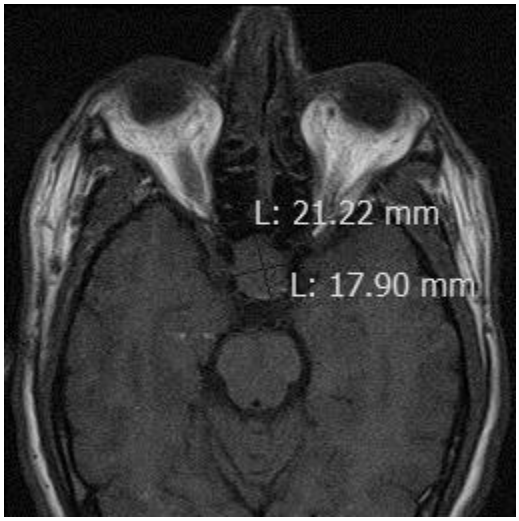

Figure 1. The pituitary sella showed a mass arising from the pituitary.

Intravenous fluids and insulin were administered for treatment of DKA. The metabolic acidosis resolved within 24 hours, and the patient was transitioned to subcutaneous insulin prior to uneventful transnasal sphenoidal resection of the mass.

Pathologic examination was consistent with a pituitary adenoma (Figure 2) with immunohistochemical stains strongly positive for synaptophysin and prolactin (Figure 3) with focal positivity for GH (Figure 4). A lesser degree of diffuse positivity was noted for follicle stimulating hormone (Figure 5). This plurihormonal immunohistochemical staining pattern (especially predominating positive staining for prolactin with only focal positive staining for GH) is well-described in some patients with pituitary adenoma and clinical acromegaly, as in this patient.[16]

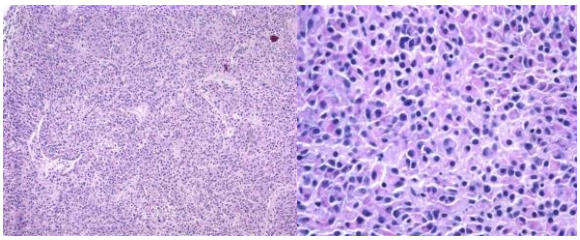

Figure 2. Pathologic examination was consistent with a pituitary adenoma.

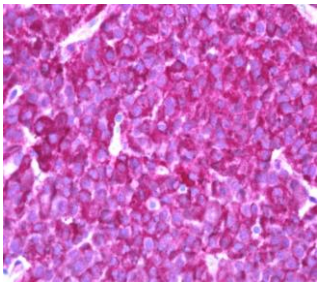

Figure 3. Immunostaining was positive for prolactin and synaptophysin.

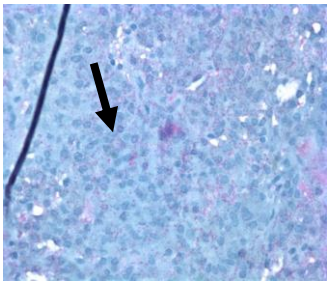

Figure 4. Immunostaining was positive for growth hormone.

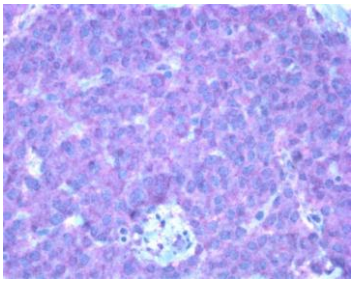

Figure 5. Immunostaining was positive for follicle stimulating hormone.

The patient was discharged on subcutaneous insulin, metformin, and lanreotide 60 mg intramuscularly monthly. At the two-month follow-up, the HbA1c level was 6.3% with a persistent elevation in the IGF-1 level at 907 ng/ml (68 - 225) and prolactin level at 50 ng/ml (4.8 - 23.3). Repeat MRI showed no evidence of residual or recurrent neoplasm. The patient was initiated on cabergoline 0.5 mg orally two times weekly for the hyperprolactinemia and lanreotide depot was increased to 90 mg intramuscularly monthly. At three months, the prolactin level had decreased to 3.2 ng/ml (4.8 - 23.3) and the IGF-1 level had decreased to 620 ng/ml (68 - 225). The lanreotide depot dose was titrated upward to achieve a normal IGF-1 level. A repeat HbA1c was 6.0% and insulin was discontinued.

Discussion

The mechanism of DKA in acromegaly is thought to be a GH and IGF-1 mediated insulin resistance in the liver and peripheral tissues leading to increased endogenous glucose production, reduced peripheral glucose uptake, and consequently hyperglycemia and β-cell glucotoxicity with reduced insulin production.[14] During fasting and other catabolic states, GH predominantly stimulates lipolysis and the release and oxidation of free fatty acids. In addition, possible direct stimulation of hepatic ketogenesis may explain diabetic ketoacidosis in some patients with acromegaly.[17] Glucagon, a counter regulatory hormone important in the pathogenesis of DKA, may be elevated in patients with acromegaly.[14]

The treatment of DM and the prevention of DKA need to be directed at decreasing GH/IGF-1 levels, either surgically or pharmacologically. Endocrine remission occurs in 50% of GH-secreting macroadenomas after surgery.[18] Patients with acromegaly and DKA showed resolution of the DKA with standard medical therapy and reduced insulin requirements and oral hypoglycemic medications after trans-sphenoidal surgery in previous case reports.[3-15] These patients required insulin for 1-20 weeks post trans-sphenoidal surgery.

Our patient improved with the standard therapy for DKA with IV and subcutaneous insulin, IV fluids, and electrolyte replacement. Subcutaneous insulin was stopped three months after surgery. Our patient had a plurihormonal adenoma producing both GH and prolactin. Cabergoline normalized her prolactin levels within three months. The elevation in her IGF-1 level required escalation of the lanreotide depot dose. The clinical course of our patient was comparable to many cases previously reported with DKA and acromegaly that underwent trans-sphenoidal pituitary adenoma resection.[3-15]

Conclusion

The definitive treatment of acromegaly is an important part of glycemic control in acromegalic patients presenting with DKA. There is need for further studies to evaluate the effect of somatostatin analogues and somatotroph tumor resection in the prevention of DKA in the long term.

References

[1] Chanson P, Salenave S. Acromegaly. Orphanet J Rare Dis 2008; 3:17. PMID: 18578866.

[2] Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. Pituitary 1999; 2(1):29-41. PMID: 11081170.

[3] Palakawong P, Arakaki RF. Diabetic ketoacidosis in acromegaly: A case report. Endocr Pract 2012; 1-15. PMID: 23186966.

[4] Mewawalla P, Jaiswal G, Moustakakis M, Sankaranarayanan N, Dasanu CA. Refractory DKA as first presentation of acromegaly and a potential role for continuous venovenous hemofiltration in its successful management. Conn Med 2011; 75(7):405-407. PMID: 21905534.

[5] Erem C, Ersöz HO, Ukinç K, Avunduk AM, Hacihasanoglu A, Koçak M. Acromegaly presenting with diabetic ketoacidosis, associated with retinitis pigmentosa and octreotide-induced bradycardia: A case report and a review of the literature. Endocrine 2006; 30(1):145-149. PMID: 17185803.

[6] Westphal SA. Concurrent diagnosis of acromegaly and diabetic ketoacidosis. Endocr Pract 2000; 6(6):450-452. PMID: 11155217.

[7] Yoshida N, Goto H, Suzuki H, et al. Ketoacidosis as the initial clinical condition in nine patients with acromegaly: A review of 860 cases at a single institute. Eur J Endocrinol 2013; 169(1):127-132. PMID: 23653454.

[8] Carrasco de la Fuente M, González-Albarrán O, Pérez López G, Cano Megías M. [Diabetic ketoacidosis as the first manifestation of a mixed growth hormone and prolactin-secreting tumor.] Endocrinol Nutr 2010; 57(10):507-509. PMID: 20705526.

[9] Waterhouse M, Sabin I, Plowman N, Akker S, Chowdhury TA. A "growing cause" of diabetic ketoacidosis. BMJ Case Rep 2009; 2009. PMID: 21686404.

[10] Kopff B, Mucha S, Wolffenbuttel BH, Drzewoski J. Diabetic ketoacidosis in a patient with acromegaly. Med Sci Monit 2001; 7(1):142-147. PMID: 11208511.

[11] Szeto CC, Li KY, Ko GT, et al. Acromegaly in a woman presenting with diabetic ketoacidosis and insulin resistance. Int J Clin Pract 1997; 51(7):476-477. PMID: 9536592.

[12] Katz JR, Edwards R, Khan M, Conway GS. Acromegaly presenting with diabetic ketoacidosis. Postgrad Med J 1996; 72(853):682-683. PMID: 8944212.

[13] Vidal Cortada J, Conget Donlo JI, Navarro Téllez MP, Halperin Rabinovic I, Vilardell Latorre E. [Diabetic ketoacidosis as the first manifestation of acromegaly]. An Med Interna 1995; 12(2):76-78. PMID: 7749014.

[14] Simmons LR, Hughes K, Markovic TP, Chua EL. Diabetic ketoacidosis as a presenting feature of acromegaly: When excess hormone meets hormone deficiency. Clin Diabetes 2012; 30(4):170-172.

[15] Lakhotia M, Mathur R, Singh H, Gahlot A,Tiwari V, Gahlot RS. Diabetic ketosis as a presenting feature of acromegaly. J Assoc Physicians India 2007; 55:377-378. PMID: 17844701.

[16] Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur J Endocrinol 2007; 156(2):203-216. PMID: 17287410.

[17] Møller N, Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev 2009; 30(2):152-177. PMID: 19240267.

[18] Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: Epidemiology, pathogenesis, and management. Endocr Rev 2004; 25(1): 102-152. PMID: 14769829.

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