Diabetic Ketoacidosis as a Presenting Feature of Acromegaly: When Excess Hormone Meets Hormone Deficiency

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In patients with acromegaly, diabetes, which is usually neither severe nor symptomatic, occurs commonly and can often be controlled with oral hypoglycemic agents. A subgroup of patients with acromegaly exhibit severe hyperglycemia and require insulin. Diabetic ketoacidosis (DKA) is rare. We present here the case of a young woman admitted to the hospital with DKA, as her initial presenting feature of acromegaly. This case illustrates the importance of considering an underlying cause, other than type 1 diabetes, as the precipitant of DKA, particularly in individuals with severe insulin resistance requiring large amounts of insulin.

PRESENTATION

S.T., a 27-year-old woman, presented to our emergency department with a history of new-onset nausea, vomiting, polyuria, polydipsia, malaise, and weight loss and a 3-month history of amenorrhea. She reported no significant medical history, no previous hospitalizations, no regular medications, and no family history of diabetes. She was afebrile but tachycardic at 110 bpm, with a blood pressure of 130/70 mmHg. Results of laboratory investigations on admission included a blood glucose of 423 mg/dl, pH of 7.25, bicarbonate of 252 mg/dl, glycosuria, and 4+ ketonuria on urinalysis.

A provisional diagnosis of new-onset diabetes with moderate DKA was made. She was admitted to the intensive care unit. Normal saline rehydration and insulin infusion were started as per our institution’s DKA protocol. Her acidosis resolved within 48 hours, and the insulin was changed to a subcutaneous basal-bolus regimen. Her insulin requirements remained unusually high for a patient with type 1 diabetes in that she required insulin glargine, 60 units at bedtime, and insulin aspart, 20 units three times daily before meals.

Her high insulin requirements prompted the addition of metformin and a more extensive evaluation for a cause of her insulin resistance. Physical examination revealed disproportionately large hands and feet with thickening of the soft tissue. S.T. also reported an increase in hand and shoe size. No arthritis, goiter, carpal tunnel syndrome, macroglossia, acanthosis nigricans, or skin tags were noted, and her teeth spacing was normal. In addition, tests for both insulinoma antigen 2 and anti–glutamic acid decarboxylase antibodies were negative.

Suspicion of acromegaly was confirmed on the basis of biochemical and imaging findings. Growth hormone (GH), at 148 mU/L (reference

Figure 1. a: Preoperative MRI shows a non-enhancing oval sellar and suprasellar mass with compression of the normal pituitary tissue. b: Postoperatively, the large pituitary tumor was resected. There remained enhancing pituitary gland in the floor of the sella with expansion of the sella from the large macroadenoma, which has been removed.
range < 28), and insulin-like growth factor 1 (IGF-1), at 105.2 nmol/L (reference range 17–42), were markedly elevated. Pituitary magnetic resonance imaging (MRI) showed a non-enhancing oval sellar and suprasellar mass (21 × 12 × 17 mm) extending to, but not compressing, the optic chiasm (Figure 1). Visual field testing revealed normal vision, no evidence of papilloedema, and a mild temporal scotoma. Additional laboratory findings included a mildly elevated prolactin of 21.2 ng/ml (reference range 2–20). The remainder of her pituitary profile was normal.

S.T. underwent a transphenoidal adenohypophysectomy, and histopathology showed a pituitary tumor (WHO 2007, Grade 1 adenoma). Immunohistochemistry stained with strong cytoplasmic positivity for GH in 50% and prolactin in 10% of tumor cells.

Her blood glucose levels normalized postoperatively with complete resolution of diabetes, and insulin was ceased. Hydrocortisone was discontinued before discharge because of normal early morning cortisol levels. A follow-up MRI showed resection of the large pituitary tumor with a normal pituitary gland in the floor of the expanded sellar (Figure 1). Postoperatively her IGF-1 level failed to normalize, and GH (3.1 mU/L) failed to suppress completely during a 75-g oral glucose tolerance test (OGTT). She is currently receiving treatment with a long-acting somatostatin analog, remains well, is asymptomatic, and continues to be monitored on a regular basis.

QUESTIONS
1. What is the incidence of diabetes in patients with acromegaly?
2. What mechanisms are thought to be involved in the development of DKA in patients with acromegaly?
3. What conditions, other than type 1 diabetes, need to be excluded as the underlying cause of DKA?

COMMENTARY
Insulin resistance, glucose intolerance, and diabetes are commonly seen in patients with acromegaly. Overt diabetes is reported to develop in ~10–50% of patients, with the percentage reported differing widely among studies.\(^2\)–\(^5\) An analysis of the risk factors promoting glucose intolerance in acromegaly by Nabarro\(^6\) revealed that higher GH levels, older age, and longer duration of disease predicted a tendency to develop symptomatic diabetes. A further study in 2001\(^7\) examined the possible risk factors for glucose intolerance in active acromegaly and found only family history of diabetes and hypertension to have significant promoting effects.

Evidence suggests that both GH and IGF-1 excess can induce insulin resistance directly in the liver, adipose tissue, and muscle, leading to increased endogenous glucose production, decreased muscle glucose uptake, and rising blood glucose levels.\(^8\)–\(^9\) Elevated levels of these hormones in the presence of relative insulin deficiency are thought to lead to DKA. DKA therefore develops in the presence of an absolute or relative deficiency of insulin together with increased levels of counterregulatory hormones (cortisol, catecholamines, glucagon, or GH). The ongoing high levels of glucose secondary to S.T.’s undiagnosed acromegaly are likely to have contributed to glucotoxicity and β-cell failure.

Furthermore, it has been proposed that high GH levels may inhibit fatty acid metabolism, increasing lipolysis and leading to ketosis.\(^1\) Glucagon has also been considered as a possible contributing factor to DKA and may be increased in acromegaly. Excessive glucagon reduces hepatic fructose 2,6 biphosphate, a metabolite that inhibits gluconeogenesis in the liver and also induces hepatic ketogenesis.\(^10\) Together with insulin deficiency, glucagon may therefore play a role in the pathogenesis of DKA in acromegaly. Increased levels of GH and glucagon, even in the presence of insulin, may be enough to shift the balance towards ketogenesis and ultimately DKA.

When acromegaly is treated, diabetes will often resolve with normalization of the patient’s OGTT. Patients with a shorter duration of acromegaly and lower GH levels before surgery are more likely to show a reversal of their impaired glucose tolerance.

In our patient, ketosis improved with insulin therapy, and complete resolution of her diabetes occurred after transphenoidal adenohypophysectomy. Resolution of her hyperglycemia was confirmed with a formal OGTT, capillary blood glucose monitoring, and a normal A1C result of 5.3%.

This case highlights the importance of investigating patients for causes of DKA other than type 1 diabetes. Apart from acromegaly, other rare causes of DKA that should be considered include type 2 diabetes with significant intercurrent stress, illness, or infection; glucocorticoid excess in Cushing’s syndrome; glucagonoma; somatotinoma; antipsychotic drugs (clozapine and olanzapine); alcohol; and pancreatitis. Early identification of an underlying cause will ensure that prompt and appropriate investigation and medical and surgical management achieve a positive outcome with possible complete resolution of diabetes.

CLINICAL PEARLS
• In patients who present with DKA and are not known to have diabetes,
it is important to consider possible underlying causes of DKA other than type 1 diabetes, particularly in individuals with severe insulin resistance requiring large amounts of insulin.
• Rare causes of DKA that should be considered include type 2 diabetes with significant intercurrent stress, illness, or infection; acromegaly; glucocorticoid excess in Cushing’s syndrome; glucagonoma; somatostatinoma; antipsychotic drugs (clozapine and olanzapine); alcohol; and pancreatitis.
• In a patient suspected of having acromegaly as the underlying cause of DKA, GH and IGF-1 levels should be measured and a pituitary MRI should be performed.
• DKA as the presenting feature of acromegaly is a rare occurrence with a favorable outcome and often complete resolution of the diabetes once the acromegaly is treated.

REFERENCES

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