CLINICAL VIGNETTE

Ketosis-Prone Diabetes: A Diagnosis That Should Be Considered During the First Presentation of Diabetic Ketoacidosis

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Case 1

A 34-year-old Hispanic man with obesity and hypertension presented to primary care with one month of urinary frequency, nocturia, extreme thirst, dry mouth, severe fatigue and one week of nausea. He had gained 30 pounds in the preceding 2 years. His paternal grandfather had type 2 diabetes and multiple family members were overweight or obese. Laboratory evaluation showed normal complete blood count, sodium 131mmol/L, potassium 6.1mmol/L, normal kidney function, glucose 626mg/dL, HbA1C 12.9%, 3+ urinary glucose, 1+ urinary ketones, and urinary specific gravity 1.032.

The patient was sent to the emergency department. He was diagnosed with new onset diabetes and diabetic ketoacidosis (DKA) and admitted for further care. He was given intravenous insulin and intravenous fluids. He received insulin teaching and was discharged on subcutaneous glargine insulin 25 units nightly and lispro insulin 8 units before meals.

About 1 month later, the patient presented to endocrinology clinic. He reported improved energy and resolution of his thirst and urinary symptoms. He was injecting insulin as prescribed. In the preceding week, his fasting glucose ranged from 135-207 mg/dL and his pre-meal glucoses ranged from 101-185 mg/dL. The patient started on regular exercise and moderated his carbohydrate intake. On exam, his weight was 235 pounds (body mass index (BMI) 34.7 kg/m^2). He had mild posterior neck acanthosis and a normal foot exam. He was started on metformin 500 mg daily and his insulin doses were reduced.

Testing revealed glutamic acid decarboxylase-65 (GAD-65) antibodies >250 IU/mL (0-5), negative islet antigen-2 (IA-2) antibodies, C-peptide 10.6 ng/mL (1.1-4.3; glucose 171 mg/dL), and a normal urinary albumin/creatinine ratio.

One month later, the patient's metformin dose had been increased to 500 mg twice a day, mealtime lispro insulin had been stopped, and nightly glargine insulin had been reduced to 10 units. His glucoses were 79-138 mg/dL, with an average glucose of 116 mg/dL. His glargine insulin was completely discontinued. Follow up glucoses 1 week later ranged from 83-135 mg/dL. The patient remains on metformin alone without recurrence of hyperglycemia or hyperglycemia symptoms or DKA.

Case 2

A 53-year-old African American male with hypertension, hyperlipidemia, obesity, and type 2 diabetes presented to the hospital with 2 weeks of polyuria and blurry vision. He was found to be in DKA with glucose >600 mg/dL and an elevated anion gap. He had been diagnosed with type 2 diabetes 1 year prior with A1C 6.7% on routine labs and was taking metformin 500 mg daily prior to the hospitalization. His paternal grandmother had type 2 diabetes. The patient was admitted for DKA management with IV insulin and eventually discharged on insulin glargine 35 units daily, insulin lispro 15 units with meals, and metformin 1000 mg twice daily.

On endocrine follow up visit, the patient was obese (BMI 36.2 kg/m^2) with mild neck acanthosis nigricans. He had negative GAD-65 antibodies, negative IA-2 antibodies, C-peptide 1.8 ng/mL (1.1-4.3; glucose 111 mg/dL), HbA1C 11.1%. He was started on dulaglutide and 1 month later, his insulin lispro was discontinued. After implementing lifestyle modifications, he was also able to stop his insulin glargine 10 months after his initial hospitalization for DKA.

After 3 months without any insulin use, the patient achieved an HbA1C of 6.3% on metformin 1000 mg twice daily and dulaglutide 1.5 mg weekly. However, 6 months after discontinuation of insulin, he developed polyuria and noticed his home glucoses were >300 mg/dL despite adherence to his medications. He recalled being treated for a skin infection several weeks prior to the onset of symptoms and admitted to not consistently monitoring his glucoses for the preceding 3 months. He was resumed on insulin glargine 20 units daily and insulin lispro 10 units with meals. Four days after resuming insulin, lab evaluation showed his beta-hydroxybutyrate was mildly elevated 3.3 mg/dL (<3mg/dL), glucose 290 mg/dL, with normal anion gap, HbA1C 10.5%, and C-peptide 2.2 ng/mL. His regimen was modified to insulin glargine 50 units daily, insulin lispro 20 units plus sliding scale with meals, metformin, dulaglutide, and pioglitazone. One month later, his glycemic control had improved and he was able to lower his insulin doses, but he remained on insulin.

Discussion

Ketosis-prone diabetes (KPD), previously also called "Flatbush diabetes" was first used to describe cohorts of African American patients who presented with DKA at the time of

diabetes diagnosis with features of type 2 diabetes and were able to discontinue insulin therapy a few months after initial presentation.[1] KPD was thought to be more common in middle-aged African American males, who were overweight to obese and had a family history of type 2 diabetes. However, KPD has now been increasingly identified in other ethnic groups, including Hispanics, Asians, and Indian Asians,[2] and in younger patients.[3]

KPD is characterized by the acute onset of severe beta cell dysfunction with a variable clinical course. The exact mechanism of ketosis remains unknown.[4] The recent "Aβ" classification of KPD, which categorizes KPD based on the presence of autoantibodies as well as beta cell reserve status, may help predict long-term insulin dependence 12 months after the index DKA episode[5] and provides some insight into the heterogeneity of KPD. An analysis of 103 cases of KPD showed that 50% were A-β+ (autoantibodies absent, beta cell function intact), 11% were A+β+ (autoantibodies present, beta cell function intact), 17% were A+β- (autoantibodies present, beta cell function absent), 22% were A-β- (autoantibodies absent, beta cell function absent). After 12 months, 100% of patients with absent beta cell function (the A+β- and A-β- groups) remained on insulin while approximately 50% of patients with intact beta cell function (the A+β+ and A-β+ groups) were able to stop insulin,[5-6] suggesting that beta cell function shortly after index DKA can be predictive of beta cell reserve in future.

Utilizing the Aβ classification, our case 1 patient is A+β+ with the presence of GAD-65 autoantibodies but very high C-peptide levels. He has insulin resistance with good beta-cell reserve and he was able to discontinue insulin and maintain good glycemic control on lifestyle modification and metformin. However, with the presence of autoantibodies, he will need close monitoring for next few years, as 50% of these patients may develop beta cell loss in future and may require insulin in 12-60 months.[7]

Our case 2 patient falls into the A-β+ group, the group that is also called ketosis-prone type 2 diabetes, as clinical and biochemical characteristics are most similar to type 2 diabetes.[7] A-β+ is the largest group of KPD, that has substantial beta cell functional reserve shortly after DKA, and more than 70% of these patients were able to achieve insulin independence in 4-8 months after index DKA in a large cohort study.[8] This group can be further categorized into two subsets, depending on whether DKA is provoked or unprovoked; the provoked DKA group patients appear to have less beta cell reserve in longitudinal studies and higher frequency of the HLA allele associated with type 1 diabetes, compared to the unprovoked DKA group.[9] Given the relapse of ketosis in case 2 was suspected to be provoked by cellulitis, the patient in case 2 may have less beta cell reserve than initially thought and thus maybe at increased risk of requiring long term insulin treatment. His beta cell function will be re-assessed before insulin discontinuation can be considered in future.

Despite presenting acutely with DKA, many of newly diagnosed diabetes patients who are obese and have clinical and immunogenic features of type 2 diabetes may fall into the KPD classes (A+β+ and A-β+) that can discontinue insulin therapy during follow up. It is recommended that these patients continue insulin therapy for the first 2-10 weeks after their DKA episode and assess for autoantibodies and beta cell reserve by checking fasting C-peptide and glucose levels. Patients who have intact beta cell function and achieve good glycemic control can be considered for withdrawal of insulin. If glycemic control is suboptimal with lifestyle modification, it is recommended to start metformin and other insulin-sensitizing anti-diabetic medications as they can prolong the need to add or restart insulin.[10] It is also crucial that patients be educated on the signs and symptoms of DKA and how to monitor glucoses and ketones at home, as relapses of DKA can occur, and patients will need to resume insulin therapy when it does.

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