

Diabetic Ketoacidosis as The First Manifestation of a Young Adult with Diabetes: A Clinical Approach to Distinguish Different Types of Diabetes Mellitus

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ABSTRACT

Diabetic ketoacidosis (DKA) is an acute metabolic complication of diabetes. While it most commonly occurs in type 1 diabetes (T1DM), DKA can also occur in other types of diabetes. Encountering a case of DKA prompts further evaluation to determine the type of diabetes and manage patients accordingly. To establish a diagnosis of the type of diabetes in a case with an unusual presentation of DKA through a clinical approach. A 30-year-old male presented to the emergency department with sudden dyspnea. Laboratory examinations showed a blood glucose level of 506 mg/dL, a blood ketone level of 2.6 mmol/L, and a bicarbonate level of 5 mEq/L. His hemoglobin A1c was 15.3%. He had not been previously diagnosed with diabetes mellitus. Studies have shown overlapping clinical and biochemical parameters of DKA among various types of diabetes. Following life-saving management, further clinical and laboratory evaluations should be performed. Measurement of autoantibody titer (i.e.: autoantibodies against glutamic acid decarboxylase, islet antigen-2, zinc transporter 8, and insulin) and c-peptide levels might help determine the type of diabetes in this patient. Establishing the diagnosis of a certain type of diabetes in young adults can be challenging. Based on clinical profile, a presumptive diagnosis of autoimmune diabetes, particularly latent autoimmune diabetes in adults (LADA), was made in this patient.

Keywords: Diabetes mellitus, diabetic ketoacidosis, latent autoimmune diabetes in adults, young adult

INTRODUCTION

One of the most severe acute metabolic complications of diabetes is diabetic ketoacidosis (DKA), characterized by a triad of hyperglycemia, ketonemia, and high anion gap metabolic acidosis.¹ These conditions can lead to dehydration, coma, and death.² The American Diabetes Association (ADA) classifies diabetes into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and other specific types of diabetes.³ Although DKA is typically associated with T1DM, it can also occur in other types of diabetes.^{4,5} DKA is a life-threatening complication that can be prevented.⁴ Glycemic control intervention should be tailored to the individual patient's needs and diabetes type.^{2,3} Therefore, encountering a case of DKA, especially with unusual presentations, necessitates further evaluation to appropriately manage patients and avoid unnecessary therapy.

CASE ILLUSTRATION

A 30-year-old male presented to the emergency department with an acute onset of dyspnea 6 hours prior to admission. The shortness of breath was continuous, not affected by body position, and not associated with edema. There was no complaint of cough nor fever. His current complaint was accompanied with general weakness, nausea, and vomiting. There were no complaints of dysuria or diarrhea. There was no significant past medical history other than a growing mass on his right upper arm, suspected to be osteosarcoma. This mass developed after a fracture that occurred 4 months prior to admission. The patient was not taking any routine medication and had not received any corticosteroid treatment for his right humeral mass prior to the current admission. Furthermore, the patient reported experiencing polydipsia, polyuria, and a significant weight loss (30 kg) for the last 4 months. He had been previously obese (body

mass index/BMI 30 kg/m²). The patient's family history revealed a diabetic father, diagnosed at the age of 38, and has been receiving insulin treatment ever since. There was no grandparental history of diabetes.

On arrival, the patient's vital signs were within normal limit other than tachycardia and a rapid deep breathing pattern. His BMI was 17.6 kg/m² (underweight). A thorough physical examination did not reveal any lung and heart abnormalities. There was a mass in his right humerus along with restricted range of motion. Examination of other organs were unremarkable. The complete blood count showed leukocytosis (27.700/ μ L) and neutrophilia (86%), while the biochemistry examination showed a high random blood glucose level of 506 mg/dL, high hemoglobin A1c (15.3%), a high blood ketone level of 2.6 mmol/L, and a low bicarbonate level of 5 mEq/L. The amylase, lipase tests were increased below threefold of upper normal limit. Renal function, and liver function tests were within normal limit. His urinalysis displayed glucosuria and ketonuria. There were no radiological abnormalities of the heart and lungs from chest radiograph. Electrocardiography showed sinus tachycardia of 140 beats per minute with no other abnormalities.

The patient was diagnosed with diabetic ketoacidosis (DKA) and received intravenous fluid hydration as well as intravenous insulin infusion. Subsequently, he was admitted to the high care unit. Throughout hospitalization, his condition gradually improved and successful blood glucose control was achieved with subcutaneous fixed-dose insulin. Additional examinations showed a low c-peptide level of 0.11 ng/mL and a negative glutamic acid decarboxylase (GAD) autoantibody of <5.0 IU/mL in this patient. The biopsy of his right arm showed histological findings of high-grade sarcoma suggesting an osteosarcoma. The patient was discharged with a fixed-dose subcutaneous insulin therapy.

DISCUSSION

The diagnostic criteria for diabetes include several parameters that reflect the condition of hyperglycemia, which are: fasting plasma glucose ≥ 126 mg/dL, or two-hour plasma glucose ≥ 200 mg/dL during oral glucose tolerance test, or A1c $\geq 6.5\%$, or a random plasma glucose ≥ 200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.³ In the patient of our case, we found the classic symptoms of hyperglycemia: polydipsia, polyuria, and unintentional weight loss. He also fulfilled other criteria such as A1c $\geq 6.5\%$ and a presentation of hyperglycemic crisis (DKA).

DKA, an acute metabolic complication of diabetes mellitus, consists of the triad of hyperglycemia (defined as blood glucose >250 mg/dL), ketonemia, and high anion gap metabolic acidosis (bicarbonate <18 mEq/L and anion gap >12).¹ The patient of our case fulfilled the criteria of DKA as shown by his laboratory parameters: elevated blood glucose level (506 mg/dL), increased plasma ketone level (2.6 mmol/L), and high anion gap (25 mEq/L), as well as decreased bicarbonate level (5 mEq/L). The age at onset of DKA in our patient was in the early adulthood, making his diabetes type

obscured. DKA was once thought to be a pathognomonic feature of T1DM. This concept has now been reformed as DKA can also be found in T2DM, despite occurring most often in T1DM.^{3, 5-7} Another traditional paradigm of T1DM occurring only in children and T2DM being exclusive to adults is also no longer valid as the onset of T1DM may appear in adulthood.³ In patients who present with DKA, a thorough investigation is recommended for correct diabetes categorization and to determine the lifelong therapy of diabetes.⁸ With the challenges in identifying diabetes type, several studies have reported the comparison between DKA in T1DM and T2DM (Table 1). A variety of clinical and laboratory parameters overlapped between DKA in T1DM and T2DM.^{5, 6, 8, 9} There is no single marker yet that can distinguish one type from the other. Therefore, we were not able to conclude the diabetes type of our patient up to this point. One clinical algorithm (Figure 1) demonstrates a simple method to determine some commonly encountered diabetes types. Moreover, given the age of our patient was in the young adult category, we also evaluated our patient based on a list of clinical features of several diabetes types that are relevant to our patient (Table 2).

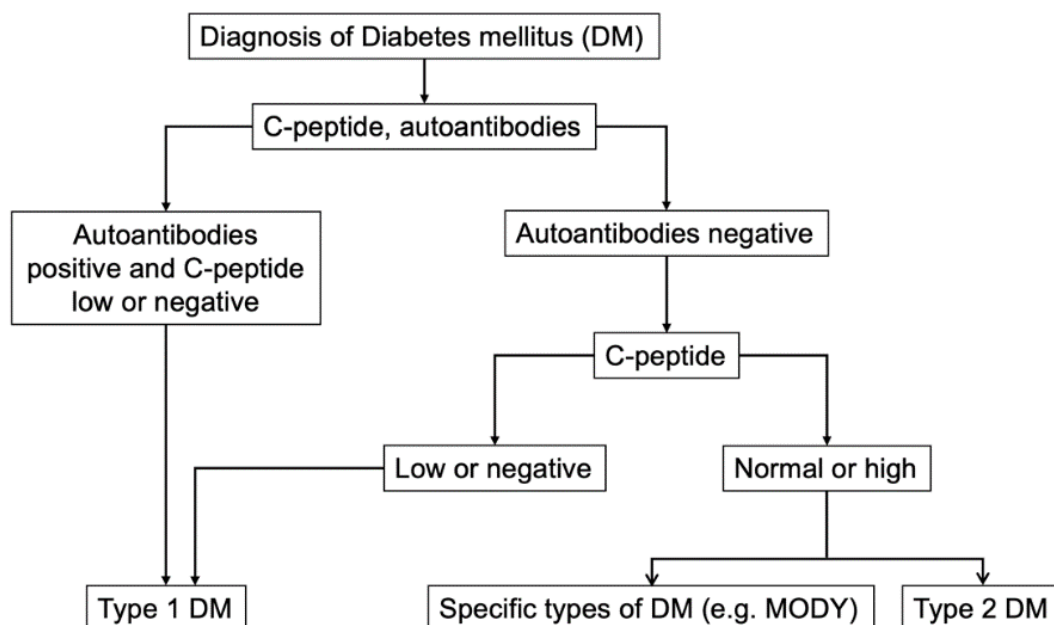


Figure 1. Clinical algorithm for classification of diabetes mellitus.

Adapted from: Hörber S, Achenbach P, Schleicher E, Peter A. Harmonization of immunoassays for biomarkers in diabetes mellitus. *Biotechnol Adv.* 2020; 39:107359.

Table 1. DKA in T1DM vs. T2DM

	Newton, et al. ^a			Barski, et al. ^c			Wang, et al. ^b			Tan, et al. ^a		
	T1DM	T2DM	p-value	T1DM	T2DM	p-value	T1DM	T2DM	p-value	T1DM	T2DM	p-value
Age on admission (years)	38.2 ± 13.3	42.5 ± 3.3	NS	37.3 ± 16.1	64.3 ± 12.4	<0.001	36.9 ± 3.2	63.0 ± 6.0	0.003	30.24 ± 15.14	56.51 ± 14.05	?
Precipitating factor:												
Insulin-related, n (%)	-	-	-	83 (50)	3 (86)	<0.001	-	-	-	-	-	-
Infection, (%)	? (22)	? (48)	?	49 (29.5)	14 (40)	0.02	4 (50)	10 (56)	NS	-	-	-
BMI >25 kg/m ² , n (%)	? (21)	? (70)	?	-	-	-	5 (28)	5 (63)	NS	3 (7.30)	63 (35.39)	?
Baseline ischemic heart disease, n (%)	-	-	-	14 (8.4)	12 (34.3)	<0.001	-	-	-	-	-	-
Blood glucose (mg/dL)	461.4 ± 192.3	396.6 ± 191.1	?	543 ± 181	646 ± 250	0.026	651.6 ± 66.6	693 ± 59.4	NS	367.56 ± 231.1	324.54 ± 195.48	?
Bicarbonate (mEq/L)	9.8 ± 5.0	12.0 ± 4.6	?	10.9 ± 3.9	9.7 ± 4.5	0.1	8.0 ± 1.1	13.4 ± 1.9	0.031	-	-	-
Arterial pH	7.19 ± 0.14	7.28 ± 0.03	< 0.1	7.18 ± 0.11	7.14 ± 0.17	0.1	7.11 ± 0.04	7.23 ± 0.06	0.099	7.336 ± 0.158	7.389 ± 0.094	0.028
Creatinine (mg/dL)	1.2 ± 0.5	1.2 ± 0.3	?	1.18 ± 0.78	1.53 ± 0.89	0.036	1.35 ± 0.18	1.62 ± 0.24	NS	-	-	-
Leukocyte (x 10 ³ /μL)	14.1 ± 7.3	10.0 ± 1.3	< 0.1	15.7 ± 7.1	15.6 ± 8.5	0.9	-	-	-	-	-	-

?: not stated; BMI: body mass index; NS: not significant; T1DM: type 1 diabetes; T2DM: type 2 diabetes.

Autoantibodies against a variety of β -cell components are important biomarkers. These include autoantibodies against glutamic acid decarboxylase, islet antigen-2, zinc transporter 8, and insulin.² Although common in T1DM, these autoantibodies can occasionally be found in T2DM.² The most frequent (>70%) autoantibody in T1DM and latent autoimmune diabetes in adults (LADA) is glutamic acid decarboxylase autoantibody (GADA).¹⁰ Our patient showed a negative GADA result. This does not rule out the possibility. Of the presence of autoantibody to other β -cell components. Due to limited resources, we could not perform the evaluation of other autoantibodies. However, c-peptide measurement would still be useful for diabetes classification regardless of autoantibody result. C-peptide, a molecule generated from the proteolysis of proinsulin, has a longer plasma half-life and a more constant

blood concentration compared to insulin and is mainly used as a marker of β -cell function.¹⁰ The c-peptide level of our patient was decreased (0.11 ng/mL). In T1DM, endogenous insulin release is diminished due to autoimmune-mediated β -cell destruction. In contrast, T2DM patients have normal or increased endogenous insulin synthesis to overcome insulin resistance in the early stage of disease progression.¹⁰ However, advanced impaired glucose tolerance in T2DM may lead to β -cell insufficiency and reduced insulin and c-peptide secretion.¹⁰ Based on his age at onset and the lack of micro-/macrovascular diabetic complications, we did not consider the result of our patient as an advanced stage of T2DM but suspected that the patient has autoimmune-diabetes instead.

Table 2. Features of several types of diabetes.¹¹⁻¹⁵

	T1DM	T2DM	LADA	Monogenic diabetes
Age at onset	Commonly in childhood and early adolescence <30 years old	Adulthood, typically >25 years old	Above 30 years old	Usually before 25 years old
Family history of diabetes	Infrequent (5-10%), usually sporadic (>85%)	Strongly positive (75-90%)	Negative or positive	Positive for ≥ 3 generations
BMI	Usually thin, but can still be like general, non-diabetic population	Overweight or obese (>90%)	Normal, rarely overweight/obese	Like general, non-diabetic, population
Insulin resistance	Absent	Increased	Increased/no change	Absent
C-peptide levels	Low or undetectable after 3 years from diagnosis	Normal-high	Decreased but still detectable	Low-normal
Autoantibodies	Positive in most patients (80-90%)	Negative	Positive	Negative
Insulin dependent	Yes	No	Yes, >6 months after diagnosis	No
Risk of DKA	High	Low, except ketosis-prone subtype	Low	Low

DKA: diabetic ketoacidosis; LADA: latent autoimmune diabetes of adulthood; T1DM: type 1 diabetes; T2DM: type 2 diabetes

T1DM typically appears in childhood and early adolescence with 2 peaks of onset: age group 4–7 years old and 10–14 years old.¹⁶ Meanwhile, LADA appears in people aged 30–50 years old,¹⁷ which is more suitable for our patient. LADA has overlapping features of T1DM and T2DM.¹⁵ On one side, it is immunologically similar to T1DM although the destruction progresses at a much lower rate.¹⁸ On the flipside, it has features similar to T2DM such as onset at adulthood, subclinical/non-acute onset (e.g.: non-dramatic hyperglycemia), insulin independence (at least for the first 6 months of diagnosis), and insulin resistance.^{14,18} Patients with LADA have residual c-peptide levels between T1DM and T2DM.¹⁸ This residual endogenous insulin production portrays a slowly progressing β -cell destruction and therefore patients with LADA usually do not require insulin for the initial 6 months after diagnosis.¹⁸

We made a presumptive diagnosis of autoimmune diabetes, particularly LADA, based on the clinical profile of our patient despite no autoantibody being found (i.e.: age at onset, low c-peptide level in the absence of advanced diabetic complication signs). On one side, our patient was 30 years old, underweight, and his clinical data was in line with the diagnosis T1DM based on algorithms shown above. On the other side, our patient's history of being obese and a positive diabetic family history showed an overlapping T2DM features. These mixed features support the diagnosis of LADA. Owing to the slow progression of β -cell destruction, DKA is usually absent at diagnosis of LADA. However, our patient had demonstrated an insidious onset of diabetes by looking at his symptoms of polydipsia, polyuria, and a significant weight loss over the last 4 months prior to his DKA episode. This is also reflected by his high A1c level in contrast to the average A1c of new-onset T1DM that rarely exceeds 10%.^{19,20}

Glycemic control is a key factor for the prognosis of this patient. Patients with LADA may experience a mortality rate as high as T2DM. Chronic exposure to hyperglycemia increases the risk of micro- and macrovascular

complications.^{14,18} Chemotherapeutic agents such as doxorubicin may induce hyperglycemia. If poorly controlled, the hyperglycemic condition in this patient may in turn exacerbate chemotherapy-induced neuropathy and nephropathy.

CONCLUSION

Establishing a diagnosis of certain diabetes type in young adults remains challenging, particularly in patients with unconventional presentation. DKA is not exclusive to T1DM. Currently, there is no distinguishing DKA features that can definitively classify the type of diabetes. Although no autoantibody was found, a presumptive diagnosis of autoimmune diabetes, particularly LADA, was made in this patient based on his clinical profiles.

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