CASE REPORT

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Diagnostic Challenge of Adult-onset Type 1 Diabetes Mellitus in a Remote Hospital

Bryan Arista Hartono,[1] Joshua Henrina,[2] Doddy M. Turmudzi[1,3]
[1]Majalengka General Hospital, Majalengka, Indonesia
[2]School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
[3]Internal Medicine Department, Majalengka General Hospital, Majalengka, Indonesia

Abstract

Type 1 Diabetes Mellitus (T1DM) is a chronic endocrinological disease due to an autoimmune process. The prevalence of T1DM is 9.5% worldwide, with the incidence of 15 out of 100,000 people, ranging from childhood to 40 years of age. Autoimmunity-related late-onset Diabetes Mellitus (DM) patients could be diagnosed as classic T1DM or latent autoimmune diabetes in adults (LADA). A 30-year-old male patient with unremarkable previous medical history was admitted to the emergency room with dyspnea for the last three days that was worsened six-hour before admission. Physical examinations showed a body Mass Index (BMI) of 18.75 kg/m^2, irregular pulse, and Kussmaul breathing. The patient was diagnosed with diabetic ketoacidosis (DKA) on May 23, 2019. He was discharged with subcutaneous insulin pen injections. Two years later, he was readmitted with DKA due to discontinuing his treatment. He stated that the reason for stopping the insulin was because he was tired of injecting it. The patient was hospitalized and was discharged with oral antidiabetic agents to cope with his injection tiredness issue. One week later, the patient complained of dyspnea and was diagnosed with recurrent DKA. He was hospitalized and prescribed subcutaneous insulin. In this kind of situation, a diagnosis of LADA for patients presenting with DKA without prior history of DM in early adulthood needs to be considered. In contrast to the classic T1DM, the need for insulin occurs late in LADA. Affordable and widely available ancillary examinations are needed, including in remote hospitals. Finally, motivational support for patients is as important as the pharmacological treatment since lifelong insulin injections are needed.

Keywords: Adult onset, autoimmunity, diabetic ketoacidosis, type 1 diabetes mellitus

Introduction

Diabetes mellitus (DM) is a complex chronic disease with both short- and long-term complications that can affect a person's quality of life. Therefore, it requires excellent glycemic control through medical treatment and appropriate multifactorial risk reduction strategies.[1,2] According to the American Diabetes Association, there are four diabetes classifications, i.e., type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), specific type diabetes due to other causes, and gestational diabetes.[3] T1DM is a chronic endocrinological disorder marked by an absolute insulin deficiency due to the destruction of pancreatic beta cells from an autoimmune process.[4,5]

Corresponding Author:
Doddy M. Turmudzi
Internal Medicine Department, Majalengka General Hospital, Indonesia
Email: dmturmudzi@gmail.com

Globally, the International Diabetes Federation (IDF) stated that as many as 463 million adults aged between 20 to 79 years suffer from DM, with 79% distributed in low- and middle-income countries (LMIC).[6] Globally, the prevalence of DM patients in Indonesia is 7th in rank, with a total of 10.7 million people in 2019.[7]

Based on a meta-analysis, the global prevalence of T1DM is 9.5% with an incidence of 15 out of 100,000 people.[8] T1DM can be seen in any age, including children to adults before the age of 40 years. Nonetheless, most T1DM occurred between the age of 4 to 14 years.[9]

Patients with adult-onset DM with an autoimmune disorder similar to T1DM may have classic type 1 DM or latent autoimmune diabetes of adults (LADA).[10] LADA cases are expected in Caucasian and Asian adult populations, with 40% of cases of T1DM occurring over the age of 30 years.[11]

Compared to T1DM, LADA has presentations

more similar to T2DM patients, due to slower pancreatic beta-cell failure than T1DM despite positive islet antibodies.[11,12] These presentations can lead to a misdiagnosis and will be managed as T2DM. The slower rate of beta-cell failure in LADA versus T1DM in adults is defined by the absence of insulin therapy during the first 6 to 12 months of diagnosis. However, the criteria are dependent on the clinical decision.[13] Alternatively, a fasting c-peptide level can indicate residual insulin secretion and predict late-onset presentations.[14] Finally, glutamic acid decarboxylase antibodies (GADA) are distinct antibodies that set LADA apart from other types of DM. This report aims to increase awareness of LADA, especially in patients with adult-onset DM, from diagnosis to holistic treatment.

Case

A 30-year-old man came to the ER of Majalengka General Hospital on April 23, 2019, with a primary complaint of shortness of breath in the last three days, which worsened six hours before admission. His complaint was accompanied by unbearable epigastric pain with a pounding quality. Previously, the patient has experienced symptoms of weakness, excessive thirst and hunger, and frequent urination. The patient's weight has decreased by 12 kg in the past two months. Other than dyspepsia, his past medical history was insignificant. None of the patient's family members have had similar complaints or a history of DM, hypertension, or autoimmune disease.

The physical examinations on admission were as follows: He has a weight of 48 kg and a height of 160 cm, with a body mass index (BMI) of 18.75 kg/m^2. Vital signs showed elevated blood pressure (150/90 mmHg), tachycardic (heart rate of 125 beats/minute dan irregular), a respiratory rate of 41 times/minute with a Kussmaul pattern, and a temperature of 36.8^{o}C. His oxygen saturation was 95% on ambient air. Other physical examinations were within normal limits. Laboratory findings were consistent for hyperglycemic crisis (Table 1). Accordingly, his electrocardiogram showed atrial fibrillation rapid ventricular response with peak-tall T waves at V5 and V6 leads.

Thus, the diagnosis of hyperglycemic crisis was made, with a differential diagnosis of diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state accompanied by severe dehydration and electrolyte imbalances (hyponatremia and hyperkalemia).

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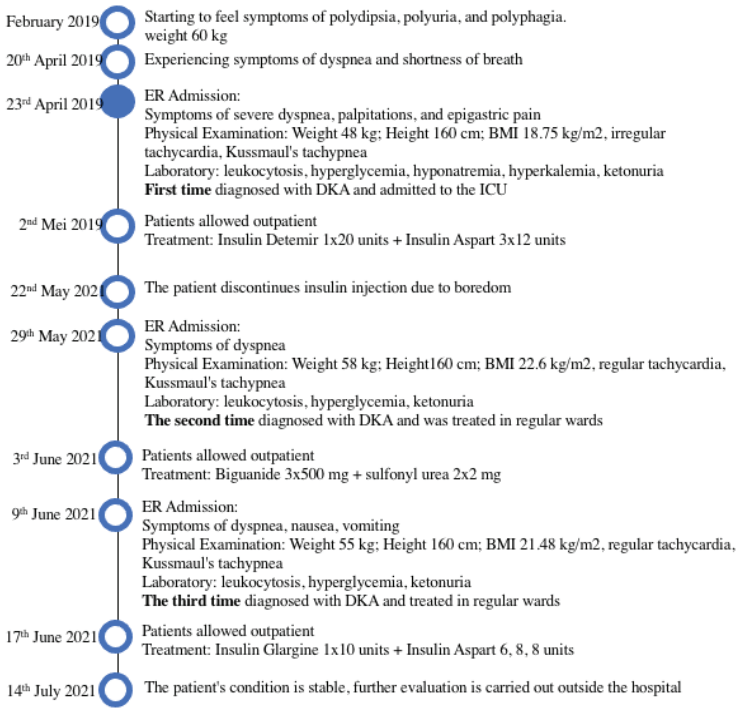

Figure 1 Patient Timeline

Table 1 Laboratory Findings on April 23 to 27, 2019

Examinations	Results		
	23rd April	**24th April**	**27th April**
Hematology			
Hemoglobin (g/dL)	15.3		14.2
Hematocrit (%)	44.5		41.0
Erythrocyte (10^3/uL)	5.32		4.96
Leucocyte (10^3/uL)	33.1		19.80
Thrombocytes (10^3/uL)	462		162
ESR (mm/hour)	5		
Blood chemical			
Random blood glucose level (mg/dL)	648		306
AST (U/L)	17		32
ALT (U/L)	24		12
Ureum (mg/dL)	86.2	42.7	106.7
Creatinine (mg/dL)	2.41	1.27	2.48
Electrolyte			
Sodium (mEq/L)	129.0	134.0	
Potassium (mEq/L)	8.3	5.1	
Chloride (mEq/L)	87.0	106.0	
Blood gas analysis			
pH			7.07
PO_2 (mmHg)			188
PCO_2 (mmHg)			14
SO_2 (%)			99
BE			-237
HCO_3^- (mEq/L)			4
Urinalysis			
Specific gravity	1.015		
pH	5.0		
Protein	Positive		
Glucose	Positive		
Ketone	Positive		
Erythrocyte	Positive		
Leucocyte	Negative		
Bacteria	Positive		

g=grams; dL=deciliter; uL=microliter; mm=millimeter; U=unit; L=liter; mEq=milliequivalent

diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state accompanied by severe dehydration and electrolyte imbalances (hyponatremia and hyperkalemia).

The patient was fasted temporarily and was given supplemental oxygen via a non-rebreathing mask at a rate of 6–15 liters per minute, fluid boluses, insulin iv drip of five units per hour, bicarbonate iv drip of 100 mEq in D5% for three hours, and insertion of a urinary catheter.

Table 2 Laboratory Examinations on April 29, 2019

Examination	Result
Hematology	
Hemoglobin (g/dL)	16.4
Hematocrit (%)	50.5
Erythrocyte (10^3/uL)	5.38
Leucocyte (10^3/uL)	27.51
Thrombocytes (10^3/uL)	496
Blood chemical	
Current glucose level (mg/dL)	727
AST (U/L)	30
ALT (U/L)	20
Uremic (mg/dL)	40.9
Creatine (mg/dL)	1.2
Urinalysis	
Specific gravity	1.015
pH	5.0
Protein	Positive
Glucose	Positive
Ketone	Positive
Erythrocyte	Positive
Leucocyte	Negative
Bacteria	Positive

g=grams; dL=deciliter; uL= microliter; mm=millimeter; U=unit; L=liter; mEq=milliequivalent

The patient was admitted to the ICU for further monitoring and received additional therapy of iv calcium gluconate 4 gr in D5% 100 ccs for three hours and antibiotics. After one day of treatment, the patient's sodium and potassium levels improved, but his blood sugar was unstable. On the fourth day, laboratory examinations and blood gas analyses were carried out, which showed compensated metabolic acidosis. Furthermore, after seven days of treatment in the ICU, he was transferred to a regular ward. He was discharged on the ninth day of hospitalization and prescribed 20 units of daily subcutaneous detemir insulin injection in the morning and 12 units of aspart insulin given three times daily subcutaneously after each meal.

Two years later, on May 29, 2021, the patient was readmitted to the ER at Majalengka General Hospital, complaining of shortness of breath. He has been abruptly stopping insulin injections for one week. Physical examinations showed a weight of 58 kg, a height of 160 cm, and a body mass index (BMI) of 22.6 kg/m^2. His blood pressure was slightly elevated (140/97 mmHg), and he was tachycardic (HR: 134 beats/minute) and tachypneic (RR: 30 breaths/minute) with a Kussmaul pattern. The laboratory findings are listed in Table 2. The patient, again, was diagnosed with DKA. The DKA was precipitated due to sudden insulin discontinuation because of boredom due to the need to inject insulin daily. The patient was hospitalized for four days and was discharged with oral anti-diabetic agents (biguanides and sulfonylurea) to circumvent patient non-adherence.

One week later, on June 9, 2021, the patient again felt shortness of breath, accompanied by nausea and vomiting three times. The physical examinations showed a weight of 55 kg, a height of 160 cm, and a body mass BMI of 21.48 kg/m^2. His blood pressure was elevated (155/104 mmHg), with a rapid heart rate (145 beats/minute) and Kussmaul respiration of 30 breaths/minute. Other findings were within normal limits. Laboratory investigations were performed (Table 3) and were consistent with a diagnosis of DKA. The patient was then treated in the regular ward with fluid rehydration therapy, subcutaneous insulin detemir 1x10 unit, insulin aspart 3x10 unit, and bicarbonate iv drip 100 meq in D5% 200 ccs for three hours. It took eight days of treatment to stabilize the patient's condition. On the eighth day of treatment (June 17, 2021), the patient was discharged with subcutaneous insulin aspart injection, with doses of 6 units in the morning and eight units in the afternoon and evening given after meals, and ten units of subcutaneous insulin glargine in the evening, once daily.

In July 14, 2021, further evaluations were carried out to determine the cause of the patient's recurrent DKA and the onset of DM in a relatively young adult. More exhaustive laboratory investigations were carried out (Table 4). As a result of the treatment, the patient's weight returned to 58 kg and a BMI of 22.6 kg/m^2.

Discussion

The incidence of DKA in patients with no previous history of DM can be found in 1 of 3 cases that occur.[15,16] The Indonesian prevalence rate of DM in the productive age group who had not been previously diagnosed with DM, was higher than those who had been diagnosed, i.e.,

Table 3 Laboratory Examination in June 9 and July 14, 2021

Examinations	Results	
	9th June	14th July
Hematology		
Hemoglobin (g/dL)	16.7	13.9
Hematocrit (%)	50.7	42.6
Erythrocyte (10^3/uL)	5.49	4.62
Leucocyte (10^3/uL)	17.46	7.1
Thrombocytes (10^3/uL)	569	386
Blood Chemical		
Current glucose level (mg/dL)	832	192
AST (U/L)	12	18
ALT (U/L)	9	14
Uremic (mg/dL)	57.8	18
Creatine (mg/dL)	2.0	0.73
eGFR (mL/min/1,73m^2)	45	123
C-peptide (ug/mL)		<0.01
HbA1C (%)		10
Total Cholesterol (mg/dL)		221
LDL (mg/dL)		146
HDL (mg/dL)		56
Triglyceride (mg/dL)		77
Pancreatic amylase (U/L)		26
Pancreatic lipase (U/L)		27
Electrolyte		
Natrium (mEq/L)	129.0	
Potassium (mEq/L)	8.3	
Chloride (mEq/L)	87.0	
Urinalysis		
Density	1.015	1.005
pH	5.0	7.0
Protein	Positive	Negative
Glucose	Positive	Negative
Ketone	Positive	Negative
Erythrocyte	Positive	Negative
Leucocyte	Positive	Negative
Bacteria	Positive	Negative

g=grams; dL=deciliter; uL=microliter; mm=millimeter; U=unit; L=liter; mEq=milliequivalent

3.5% and 1.1%, respectively.[2] Thus, there is a possibility of encountering DKA cases in patients with no previous history of DM.

Shortly, DKA occurs when there is an absolute insulin deficiency or increased insulin requirements, as in infection, which stimulates

the secretion of counterregulatory hormones. Consequently, glucose utilization decreased, with simultaneous increased in liver lipase activation, causing the breakdown of adipose tissue into free fatty acids. These components are converted into acetyl coenzyme A, which enters the Krebs cycle to produce energy and the rest is broken down into ketones. The amalgamation of gluconeogenesis, lipolysis, ketogenesis, and decreased glycolysis are the hallmarks of DKA.[15,16]

Early symptoms of DM patients are weight loss accompanied by typical symptoms of polydipsia, polyuria, and polyphagia with a concomitant increase in blood sugar levels. T1DM is often diagnosed earlier with clinical presentations of either acute symptoms of diabetes or DKA. In contrast, patients with T2DM often do not feel sick, making an early diagnosis difficult. The physical appearance of T1DM patients with a normal or underweight BMI, in contrast to their T2DM counterparts who mainly were overweight/obese.

In this case, the patient has a normal BMI and before hospital admission, has been experiencing rapid weight loss for the last two months accompanied by typical symptoms of DM. Upon further examination, the patient was diagnosed with DKA without a previous history of DM.[17,18]

In young adults, autoimmune diabetes can be either classic type T1DM or LADA. According to research by Tang et al.,[19] the prevalence of T1DM in adults aged 30 years was 5.49% in men and 6.16% in women. The majority (65%) were LADA patients. In contrast, classic T1DM is associated with several autoantibodies, including anti-islet cell (anti-ICA), anti-insulin (anti-IAAs), anti-glutamic acid dicarboxylate (GADA), and anti-tyrosine phosphatase (anti-IA2), acute onset of insulin dependency pancreatic beta-cell failure, and susceptible to DKA,20 LADA is associated with GADA antibodies with or without anti-IA2. It does not require insulin during the disease's first six months due to the slower progression of pancreatic beta-cell damage.[3,10,19]

To illustrate the pancreatic beta-cell function, C-peptide levels can be used as a predictor of insulin secretion. They can be an alternative to the GADA examination to differentiate T1DM from LADA with a sensitivity of 90.5% and a specificity of 86.9%.[21] At the early phase of the disease, in LADA patients, C-peptide can be detectable at low levels, contrary to their T1DM counterparts, which are deficient or undetectable due to the inability to secrete insulin.

Furthermore, there is mild insulin resistance in LADA but not in T1DM.[11] In this case, the patient's C-peptide levels were deficient, indicating pancreatic beta-cell damage. Nonetheless, the examination was carried out two years after the onset of the diagnosis.

Importantly, the sensitivity and the specificity of a c-peptide assay to differentiate LADA from T1DM decrease with time, with their highest at the onset of DM. C-peptide assays far from the onset have decreased specificity and sensitivity compared to early onset in differentiating the type of T1DM. Therefore, we could not confidently enforce if it is T1DM. Moreover, we did not perform an autoantibody levels examination and insulin resistance, as they were unavailable at the peripheral health facilities.

In this case, the patient's second admission occurred due to the non-adherence to subcutaneous insulin injection. According to Maureen et al.,[22] T1DM sufferers, which mainly span from adolescence to young adulthood, coincide with a period of development that is prone to exacerbations due to treatment failure. Multiple factors, such as a strict schedule, difficulty in managing lifestyle, and the need for psychosocial and environmental support, need to be considered in this group.Increasing the patient's awareness and family support is equally essential to prevent non-adherence to insulin injections.

To conclude, further examination is necessary in cases of young adult-onset DKA without a previous history of DM. A complete medical history, consisting of risk factors and complete family history that can support the development of T1DM from birth until the present, should be asked. A complete physical examination, including the patient's BMI, should be considered. At remote healthcare facilities, the C-peptide level can be utilized as an alternative ancillary test that can be used as an alternative diagnostic tool to diagnose T1DM patients presented with symptoms.

Physicians should be cognizant and vigilant of T1DM cases in young adults from the diagnosis to its management pharmacologically and non-pharmacologically to prevent the risk of acute and chronic T1DM complications.

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