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Late-onset type 1 diabetes mellitus or latent autoimmune diabetes in adults: a teachable moment.

Diabetes mellitus tipo 1 de inicio tardío o diabetes autoinmune latente del adulto: un momento educable

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ABSTRACT

Adult-onset autoimmune diabetes (AOAD) is clinical form of diabetes with a wide spectrum of genotypical and phenotypical manifestations, which has risen in prominence in recent decades, probably due to greater interest in its pathogenic mechanisms, and increased identification of autoimmune markers. The clinical presentation may vary from type 1 diabetes mellitus to latent autoimmune diabetes in adults, which although clearly distinct from a theoretical viewpoint, may pose various clinical pitfalls in practice. We present the case of a patient with AOAD which featured several diagnostic challenges during follow-up.

Keywords: Diabetes; adults; autoimmunity; diagnosis; insulin therapy.

RESUMEN

La diabetes autoinmune de inicio en la adultez es una forma clínica de diabetes que se caracteriza por un amplio espectro de manifestaciones genotípicas y fenotípicas, que ha mostrado una importante crecimiento en las últimas décadas probablemente debido a un mayor interés en sus mecanismos etiopatogénicos, así como una mayor identificación de los marcadores autoinmunes. La presentación clínica puede variar desde la diabetes mellitus tipo 1 de inicio tardío hasta la diabetes autoinmune latente del adulto, diagnósticos que si bien desde el punto de vista teórico tienen características particulares, en la práctica clínica pueden generar duda al plantearse. Por ello, se presenta el caso clínico de una paciente con manifestaciones de diabetes autoinmune de inicio en la adultez, que generó algunas diferencias diagnosticas durante el seguimiento.

Palabras clave: diabetes; adulto; autoinmunidad; diagnostico; insulinoterapia

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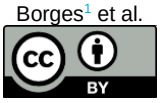

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I. INTRODUCTION

Adult-onset autoimmune diabetes (AOAD) is clinical form of diabetes with a wide spectrum of genotypical and phenotypical manifestations, which has risen in prominence in recent decades, probably due to greater interest in its pathogenic mechanisms, and increased identification of autoimmune markers. The clinical presentation may vary from type 1 diabetes mellitus (DM1) to latent autoimmune diabetes in adults (LADA). Although the latter is more frequent according to several reports, they share various pathophysiological autoimmune components, as well as the presence of insulitis (1, 2). However, the classification of these disorders is still controversial and a widely debated topic in the field of endocrinology.

The low prevalence and notable heterogeneity of AOAD in comparison with type 2 diabetes mellitus (DM2) demands a high degree of clinical suspicion to achieve early diagnosis and differentiation of the distinct forms (3). This is particularly relevant in Venezuela, in light of the severe difficulties for complementary testing and management in our region. We present the case of a patient with AOAD which featured several diagnostic challenges during follow-up.

II. CASE REPORT

A 26-year-old woman with family history of DM2 (second degree relative), consults after 5 days of dysuria with strong-smelling urine, referring generalized weakness, a burning, moderate-intensity epigastric pain with no apparent triggers or periods of remission, and dyspnea at rest of insidious onset.

On the physical examination, the patient was on bad general conditions, with tachypnea (respiratory rate: 25 bpm), fever (temperature: 39 °C), tachycardia (heart rate: 105 bpm), blood pressure of 100/65 mmHg, and body mass index of 28.5 Kg/m^2. The patient had marked dehydration, slight pallor, and ketotic breath; the cardiopulmonary examination found a Kussmaul breathing pattern, with a normal vesicular murmur in all lung fields, rhythmic heart sounds without murmurs. The abdomen was depressible and painful upon deep palpation in the epigastrium and hypogastrium, with 4 bowel sounds per minute, without signs of peritoneal irritation or visceromegaly. No neurological alterations were found.

Laboratory testing found White blood cell count 18,800 per mm^3 (neutrophils 86% / lymphocytes 13%), hemoglobin: 11.9 g/dL, hematocrit: 39%, platelets 319,000 per mm^3, random blood glucose: 390 mg/dL, urea: 21 mg/dL, creatinine: 1 mg/dL, serum sodium: 129 mmol/L, potassium: 3.4 mmol/L, chlorine: 92.8 mmol/L, calcium: 9 mg/dL, magnesium: 2.2 mg/dL, pH: 7.18; PCO2: 26.3 mmHg; PO2: 99 mmHg; HCO_3: 9.8 mmol/L, O_2 saturation: 98%. The urinalysis reported fetid and turbid general conditions, density: 1030, pH: 5, proteins: +/++++, nitrites: +/++++, ketones: +++/++++, glucose: +++/++++, bilirubin: absent, epithelial cells: 2-4 per field, leukocytes >30 per field, bacteria: abundant, pyocytes: 2-4 per field, erythrocytes: 1-2 per field.

The patient was admitted into the intensive care unit (ICU) with the following diagnoses: 1) Hyperglycemic crisis: Severe diabetic ketoacidosis (DKA), 2) Upper urinary tract infection: Acute pyelonephritis, 3) DM1. Management was based on parenteral rehydration, electrolytic correction, insulin therapy, antibiotic therapy, achieving a satisfactory evolution. She was discharged from the ICU

after 3 days, and from the medical center after 7 days. Treatment was adjusted during this time, and the patient was discharged with insulin glargine only, as she presented frequent symptomatic episodes of hypoglycemia when using preprandial rapid insulin, with glucose levels of 50-90 mg/dL. A follow-up consultation was programmed for one week after discharge; however, the patient did not attend.

Approximately 12 months later, the patient returns to the emergency department with a similar history of 3 days with dysuria and fever, and the generalized weakness with dyspnea at rest of insidious onset. The patient and her family commented she had not taken any treatment for diabetes since the previous hospitalization, as she did not agree with the diagnosis.

The clinical assessment found tachypnea (respiratory rate: 28 bpm), fever (temperature: 38 °C), tachycardia (heart rate: 115 bpm), blood pressure: 105/70 mmHg, body mass index: 27 Kg/m^2; with marked dehydration and Kussmaul breathing. The abdominal examination found hypogastric pain upon deep palpation, without peritoneal irritation. The significant findings in laboratory testing included white blood cell count: 19.800 per mm^3 (neutrophils: 84% / lymphocytes: 15%), hemoglobin: 12 g/dL, hematocrit: 40%, platelets 450,000 per mm^3, random blood glucose: 398 mg/dL, urea: 25 mg/dL, creatinine: 1.1 mg/dL, serum sodium: 133 mmol/L, potassium: 3.6 mmol/L, chlorine: 94 mmol/L, pH: 7.22; PCO_2: 28.1 mmHg; PO_2: 97 mmHg; HCO3: 9.1 mmol/L, O_2 saturation: 97%. The urinalysis reported fetid and turbid general conditions, density: 1025, pH: 5.2, proteins: +/++++, nitrites: +/++++, ketones: +++/++++, glucose: +++/++++, bilirubin: absent, epithelial cells: absent, leukocytes: uncountable, bacteria: abundant, pyocites: 4-6 per field, erythrocytes: 1-2 per field.

Therefore, the patient was admitted into the ICU again, with the same diagnoses as before, and a similar management and evolution. She was discharged with a basal insulin glargine scheme, along with occasional doses of ultra-rapid insulin (Aspart) for fasting blood glucose levels (FBG) >120 mg/dL; as its regular use during hospitalization was associated with frequent symptomatic episodes of hypoglycemia. Again, a follow-up consultation was programmed for one week after discharge.

During follow-up, the patient achieved adequate metabolic control, with FBG levels between 85-115 mg/dL and post-prandial blood glucose levels between 102-151 mg/dL; in spite of performing low levels of physical activity (<100 METS/min/week) and displaying low adherence to nutritional changes. While in treatment with 20 UI of insulin glargine, laboratory testing revealed: HbA1c: 6.9%; basal insulin: 8 UI/mL (reference values: 5 – 25), FBG: 105 mg/dL; HOMA-IR: 2.1; C-peptide: 0.66 ng/mL (reference values 0.70 – 5.2); anti-glutamic acid decarboxylase antibodies (GADAb; ELISA): 16 UI/mL (positive: >10 UI/mL), anti-insulin antibodies (ELISA): 0,21 UI/mL (positive: >1.1 UI/mL), anti-islet cell antibodies (ICA; indirect immunofluorescence): negative.

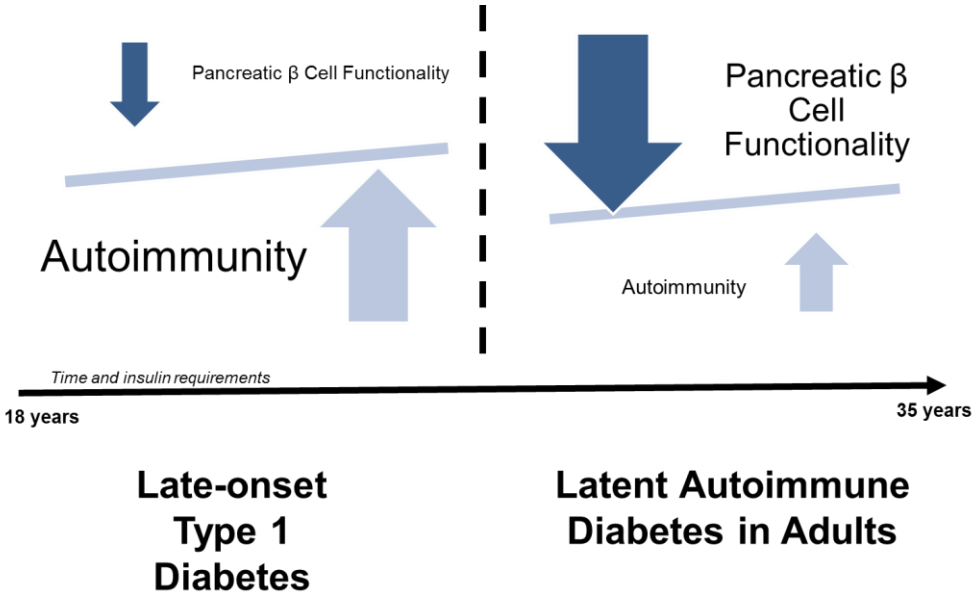
Upon these clinical and laboratory findings, we diagnosed late-onset DM1. Treatment was maintained with basal insulin glargine and occasional mealtime aspart doses. An interconsultation was also issued with department of Psychology to improve the psychosocial management, with emphasis on lifestyle changes and treatment adherence. After 2 years of follow-up, no further acute complications have occurred, and in recent weeks, the patient has begun to require lower doses of fixed mealtime aspart. Several clinicians evaluated the case and considered the diagnosis of LADA after the second hospitalization, which has motivated this report.

III. DISCUSSION AND REVIEW OF LITERATURE

This case depicts the presentation of late-onset DM1, debuting as an acute complication in association with an infection. Because of difficulties accepting the disease, a similar episode repeated months later, after which treatment adherence significantly improved. It is important to note the age of onset (26 years), which is older than the average for DM1 cases debuting with DKA (18 years) (4). This older age, along with the presence of overweight and various laboratory findings (low levels of C-peptide and GADAb) led several attending clinicians to consider the diagnosis of LADA. This is another form of diabetes which, although not recognized by the World Health Organization and the American Diabetes Association, represents the most common presentation of AOAD in some regions (1). Although LADA is a key differential diagnosis in this patient, the initial clinical manifestations render this unlikely. Here, we present various pathophysiological and clinical aspects which allow differentiation of these entities within the spectrum of AOAD.

From a molecular standpoint, DM1 develops as a result of an immune-mediated process, chiefly by autoreactive T lymphocytes, leading to the destruction of insulin-secreting cells in pancreatic islets (5). This triggers the production of ICA which can be detected in serum and establish the underlying autoimmune characteristic of this disease (6). Although not all of the related mechanisms, epitopes and triggers of this phenomena have been elucidated; the end result is a reduction in pancreatic beta cell functionality, with decreased insulin secretion which positively correlates with plasma C-peptide levels (7). In the case we present, the low levels of GADAb and C-peptide suggest the presence of a low-grade autoimmune response, typical of AOAD. However, by itself, it does not allow differentiation between late-onset DM1 and LADA (**Figure 1**).

Figure 1. Pathophysiological profile of patients with adult-onset autoinmune diabetes.



Fuente: own source

Because of this low degree of immune reactivity, it has been suggested that in AOAD, debuting with DKA is infrequent (8). However, in our experience, it is common that DM1 debuts with this complication, independently of age. In this particular case, the concurrent infections were important triggers for exacerbating the activity of the counterregulatory hormones, favoring sudden metabolic decompensation (9). The immediate requirement for insulin in 2 occasions factors against the diagnosis of LADA, considering the reformulated diagnostic criteria of the Japan Diabetes Society: 1) Presence of GADAb and/or ICA at some time during the disease course; 2) Absence of ketosis or ketoacidosis at onset (or diagnosis) of diabetes mellitus and no need for insulin treatment to correct hyperglycemia immediately after diagnosis (10, 11). **Table 1** shows the main differences between late-onset DM1 and LADA.

Regarding the treatment of our case, the requirement of insulin therapy from the beginning—which characterizes DM1—is notorious. However, the low insulin requirements after resolution of the DKA episodes and the long time between episodes without any pharmacotherapy should also be noted. This demonstrates some degree of pancreatic beta cell functionality, known as the “honeymoon” period or partial remission. The duration of this period is variable, depending of factors such as the concentrations of autoantibodies, initial levels of C-peptide, and the early age at symptom onset or development of DKA (12, 13).

Table 1. Differences between late-onset type 1 diabetes and latent autoinmune diabetes in adults.

	Late-onset Type 1 Diabetes	**Laten Autoinmune Diabetes in Adults**
Body phenotype	Normal to overweight	Variable
Onset	Acute	Rarely acute
Age at diagnosis	<18 years; rare in adulthood	>30 years
Autoimmunity	Very high	High
Antibodies	2 or more positive	At least 1 positive
Pancreatic β cell functionality	Very decreased	Decreased
C-peptide levels	Low or absent	Low
Insulin requirements	Necessary for life (<3 months)	Not during the first 6 months after diagnosis
Diabetic ketoacidosis	Present	Rare

Fuente: own source

In conclusion, this clinical case depicts a presentation within the AOAD spectrum, whose initial manifestations (DKA and immediate insulin requirement) permitted the diagnosis of late-onset DM1, in the presence of low concentrations of only one autoantibody, minimally detectable C-peptide levels, and low insulin requirements after resolution of the acute complication. The latter aspects may prompt some clinicians to contemplate the diagnosis of LADA, especially when assessing the case only after the acute decompensation has passed, and considering this entity to be more common than late-onset DM1 in various regions.

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