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Latent Autoimmune Diabetes of the Adult (LADA): a case report of a misunderstood form of diabetes

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KEYWORDS:
DM1- type 1 diabetes mellitus;
DM2- type 2 diabetes mellitus;
GAD- glutamic acid decarboxlase;
LADA- Latent Autoimmune Diabetes in Adults

Summary Latent autoimmune diabetes in adults (LADA), an increasingly recognized form of type 1 diabetes mellitus (DM1), often initially presents in middle-aged adults and is often misdiagnosed as type 2 diabetes mellitus (DM2). However, like DM1, patients often have autoantibodies directed against pancreatic islet-cells, and although ultimately they will require insulin, the progression to insulin dependence is much slower. Studies indicate that 10% of patients who present with DM2 have a positive serum glutamic acid decarboxlase (GAD) antibody titer. GAD antibody titers should be ordered for patients who do not fit the classic presentation of DM2. This is especially true in nonobese adult patients who have no family history of DM2. Studies have shown that identifying LADA patients early and initiating insulin therapy helps preserve beta cell function. The following case report will demonstrate the progression of a person who was initially identified as having DM2, but eventually was correctly diagnosed with LADA.
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Case report

History of chief complaint: A 41-year-old white male presents to the local emergency department (ED) with a worsening productive cough of one week. He also reports that he went to the ED the day before when he became anxious and dypsneic. At that time, he was treated for an upper respiratory infection and generalized anxiety with an antibiotic and short-acting benzodiazepine, respectively.

Past medical history: DM2 (diagnosed 5 years before). No history of autoimmune disorders.

Social Hx: Social drinker, no tobacco or recreational drug use.

Surgeries: Cholecystectomy.

Meds: Metformin/rosiglitazone, ezetamide, glipizide.

Family history: No history of DM2 or autoimmune disease.

Review of systems: Pertinent positives/negatives include:

respiratory: no hemoptysis, no tuberculosis exposure.
endocrine: polydipsia and polyuria over the last 10 days, and 10-lb weight loss over the last 3 weeks.

Objective findings

Vitals: BP 90/50, P102, R20, T97, O_2 saturation 98% on room air.

Caucasian, dehydrated male adult in moderate respiratory distress. He is tachycardic and has bibasilar rales and a

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fruity breath smell. No other physical examination abnormalities are appreciated.

Labs: Arterial blood gas: pH 6.95, pCO_2 11 mm Hg, PO_2 156 mm Hg, HCO_3 2 mmol/L.

CMP: potassium 5.3 mmol/L, sodium 127 mmol/L, Cl 92 mmol/L, glucose 753 mg/dL, creatinine 2.6 mg/dL, BUN 31 mg/dL.

CBC: WBC 9.5 k/μl, HBG 14.8/dL, HCT 42.3%, platelets 161 $\times$ 10^{-3}/μl

Cardiac Enzymes: CK 319, CKMB 8.2

HbA1c: 10%

Urinalysis: glucose >1000 mg/dL, ketones 40 mg/dL, protein 100 mg/dL, SP gravity 1.020, pH 5.5, nitrates-negative, leukocyte esterase–negative

EKG: sinus tachycardia; no signs of ischemia.

The normal ranges for the reported labs are: blood gas: pH (7.35-7.45), pCO_2 (35-45 mmHg), PO_2 (75-100 mmHg), HCO_3 (23-28 mmol/L).

CMP: potassium (3.6-5.0 mmol/L), sodium (135-145 mmol/L), C1 (101-111 mmol/L), glucose (70-100 mg/dL), creatinine (0.3-1.3 mg/dL), BUN (6-20 mg/dL).

CBC: WBC (5-10 K/μL), HBG (14-18/dL), HCT (40-52%), platelets (150-400 K/μL)

Cardiac Enzymes: CK (40-370 U/L), CKMB (0.3-4.0 ng/ml)

HbA1C: (4.4-6.4%)

Urinalysis: glucose (negative), ketones (negative), protein (negative), Sp gravity (1.002-1.030), pH (5-7), nitrates (negative), leukocyte esterase (negative).

Imaging studies

Chest x-ray: possible small effusion; otherwise normal.

The patient was found to have diabetic ketoacidosis (DKA). He was treated according to the medical center's DKA protocol. After discharge, the patient was sent to the Diabetes Center for specific treatment recommendations for a DM2 patient who suffered an episode of DKA.

Upon presentation to the Diabetes Center, the patient was taking only insulin glargine (Lantus®, sanofi-aventis, Bridgewater, NJ) 16 U once daily. He also had insulin Lispro (Humalog®, Eli Lilly and Company, Indianapolis, IN), but only needed this 3 to 4 times per week for intermittent hyperglycemia. Although the patient's medical history was as reported before, his initial presentation of diabetes was further investigated. Five years before the current illness, the patient experienced a 30-lb unintentional weight loss, polyuria, polydypsia, and generalized weakness. During routine laboratory evaluation at that time, the patient had an elevated glucose of 246 mg/dL, although the remainder of the labs were normal. The patient was diagnosed with DM2 and oral therapy was initiated, with glipizide, rosiglitazone, and metformin.

Since his hospitalization, the patient reported having to be very cautious about carbohydrate intake. He had limited his carbohydrates to only 30 g/day, so he would not become hyperglycemic, necessitating increased dosing of insulin. On follow-up examination, the patient had no physical signs of insulin resistance such as truncal obesity, excessive skin tags, and acanthosis nigricans. His body mass index was 21. His fasting lipids were: total cholesterol 103 mg/dL, HDL-C 73 mg/dL, LDL-C 14 mg/dL, and triglycerides 79 mg/dL. The patient was taking ezetamide at the time.

Based on his body habitus, history of DKA, classic presentation of polyuria, polydipsia, and weight loss on initial evaluation, a nondiabetic dyslipidemic lipid panel, and his lack of family history of diabetes, the patient was informed that he likely had latent autoimmune diabetes of the adult (LADA) and that the treatment for this condition would be lifetime insulin. The next step would be to order testing to evaluate his ability to make insulin (c-peptide, the marker of endogenous insulin production) as well as an assessment for autoantibodies that are present in DM1. It was agreed to allow the patient to continue his current regimen until the labs returned. However, the patient was advised that his current carbohydrate intake was inadequate for good health. The recommendation was made to attempt approximately 50% of calories as carbohydrates, whereas his was closer to 10%. The patient was also set up with diabetes education for DM1 and encouraged to focus efforts on learning about carbohydrate counting.

At his follow-up visit, a diagnosis of DM1 was confirmed, because the patient's c-peptide was low (<0.2). The pancreatic beta cells make pro-insulin, which is composed of the c-peptide that bridges the 2 chains of the insulin molecule. When the c-peptide is cleaved the insulin molecule becomes active. Insulin levels are not useful in a person who is taking exogenous insulin. However, the patient's GAD antibodies were negative. These antibodies can be positive in up to 80% of those with classic DM1, but can be absent in more than half of patients with LADA.

The patient was diagnosed with LADA based on his slow progression to insulin dependence and his current c-peptide levels. The patient reported that he had already started to feel better and was happy to be eating carbohydrates again (he had been placed on mealtime insulin with a carbohydrate:insulin ratio). It has now been 3 years since the patient's diagnosis of LADA and he is doing well on insulin pump therapy, with no further DKA episodes.

Topic discussion

LADA is a subtype of DM1. In DM1, there is beta cell destruction as a result of autoimmune response directed against pancreatic islet cells. This is verified by the presence of islet-cell autoantibodies or low c-peptide levels.[1] However, LADA patients do not immediately lose all beta cell function. This is why most LADA patients have a clinical presentation that looks more like DM2. At one time it was thought that DM1 only affected young children with insulin insufficiency and no insulin resistance, whereas DM2 affected older adults with insulin resistance but no initial insulin insufficiency.[2] It is now clear that the incidence of DM1 in patients older than 30 years is greater than previously thought.[2,3] Approximately 10% of newly diagnosed people with DM2 have autoantibodies directed against pancreatic beta cells, which eventually cause insulin insufficiency.[1,2,4,5] These discoveries led to the designation of LADA as a separate clinical entity, which was first described in 1986.[4,6]

The clinical criteria for LADA are loosely defined. The key features are: adult onset, lack of initial need for insulin therapy, and low c-peptide levels and the presence of antibodies directed against pancreatic islet cells.[7]

However, there is no clear age that defines a typical age of onset. Most clinical studies use a mean age of 30 years,[5,7] but others avoid defining a typical age at all.[1] Also, the presence of antibodies against islet cells is not specific to LADA because they are also present in DM1 and other autoimmune disorders.[8,9]

Several islet cell autoantigens are linked to DM1 including tyrosine phosphatase-like proteins IA-2 and IA-2beta,[10] glutamic acid decarboxylase autoantibodies (GADA), islet cell cytoplasmic antibodies (ICA), islet cell complement fixing autoantibodies, and insulin antibodies.[1] The autoantibody titer most commonly used to identify LADA is GAD65 autoantibody.[1,4] GAD65 is a specific 65K isoform of GAD. The presence of GAD autoantibodies and other islet cell antibodies has been associated with rapid decline of beta cell function, whereas people with DM2 without these antibodies can easily maintain beta cell function for more than 12 years after diagnosis.[4]

Studies have demonstrated that the residual beta cell function is extended with insulin therapy and shortened by insulin secretagogues.[11] It appears that exogenous insulin administration does not have an immunomodulating effect, rather it slows the loss of beta cells by reducing glucose toxicity.[3] Nevertheless, there is strong evidence that early diagnosis and appropriate treatment with insulin will delay beta cell destruction and may prevent complications.[2,4,11]

To identify and treat these patents properly, Fourlanos et al. have suggested a set of clinical criteria to determine which patients should get tested for anti-GAD65 autoantibody titers.[7] These include age <50 years, acute symptoms ("the polys"), body mass index <25, and personal history of autoimmune disease or a family history of autoimmune disease. If a patient meets two or more of these criteria, there is a recommendation that they should be tested for anti-GAD antibodies.[12] Other authors believe that a lack of family history of DM2 should be added to this list of criteria.[12]

Conclusions

This patient had an atypical presentation of DM2 and was later found to have LADA after having an episode of diabetic ketoacidosis. Most people with LADA are not identified at initial presentation. DM1 (or the LADA subtype) was a strong possibility at the initial presentation based on: (1) patient age at diagnosis (37 at that time); (2) no family history of DM2; (3) nonobese body habitus; (4) the patient's extreme sensitivity to carbohydrates; and (5) normal lipid levels. When the clinician sees a patient with these features, screening for LADA may prove to be beneficial.

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