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Latent Autoimmune Diabetes of Adult Masquerading as Type 2 Diabetes Mellitus

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Abstract

Latent autoimmune diabetes of adults (LADA) is a slowly progressing subtype of type 1 diabetes mellitus (DM) that shares features of both type 1 and type 2 diabetes mellitus (T2DM), leading to its misdiagnosis and mismanagement. We present a case of a 30-year-old man who was diagnosed and managed as T2DM but later confirmed as a case of LADA. He was sent to the endocrinology clinic by his primary care physician for management of "uncontrolled T2DM". He had been placed on glipizide and metformin, but was noted to have suboptimal blood glucose control and unintentional weight loss of about 20 - 30 lbs over a 3-month period. A diagnosis of LADA was confirmed by the presence of autoantibody to glutamic acid decarboxylase 65 (anti-GAD-65 antibody). His oral medications were discontinued and he was started on basal and mealtime insulin. It is important to identify LADA in adult patients thought to have T2DM, as these patients respond poorly to oral hypoglycemic drug therapy, require insulin and are at increased risk for developing ketoacidosis. Clinical presentation of LADA is often similar to T2DM, with diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) being uncommon complications.

Keywords: Hyperglycemia; DM; LADA

Introduction

Diabetes mellitus (DM) remains one of the commonest chronic metabolic disorders for which medical attention is sought. It has traditionally been categorized as type 1 and type 2. Type 2 diabetes mellitus (T2DM) accounts for over 90% of cases of diabetes in the United States, and other western countries, while type 1 diabetes accounts for another 5-10%, with the remainder due to other causes [1]. New information from both clinical and basic science research has led to increased understanding of genetic defects related to diabetes. Monogenic causes of T2DM (e.g., processes causing maturity onset diabetes) represent a small fraction of cases, and some commonly inherited polymorphisms by themselves contribute only small degrees of risk for, or protection from, diabetes [1].

At this time, there is increasing recognition of some other phenotypic manifestations of diabetes that do not fit exactly into the aforementioned descriptions. All these have been lumped under the "type 3" diabetes or other specific types [1].

In 1986, Groop et al [2] reported a subgroup of T2DM patients who, despite having islet autoantibodies, showed preserved β-cell function. Later, Tuomi et al [3] and Zimmet et al [4] launched the term latent autoimmune diabetes of adults (LADA) for this slowly progressive form of autoimmune diabetes. It is an increasingly recognized form of diabetes that merits proper clinical distinction to facilitate appropriate management. In these patients, early appropriate therapy may influence the speed of progression toward complete insulin dependency, and as such, efforts should be made to protect residual insulin and C-peptide secretion. LADA can serve as a model for designing new strategies for the prevention of type 1 diabetes but also provide a target for prevention in its own right [5-8].

We present a case that highlights this clinical entity and discuss some salient aspects of its management.

Case Report

A 30-year-old Caucasian male, with a history of T2DM, was referred to the endocrinology clinic for poorly controlled and labile blood sugars. He was diagnosed with T2DM 3 years earlier, at which time he was obese and was advised to lose weight, eat healthy and exercise regularly. He lost about 20 - 30 pounds of weight without much effort and thought he was doing well until he was found to have high blood sugars on routine blood work, 3 months prior to his index visit to the endocrinology clinic. He was initially started on glipizide by his primary care physician, a regime to which he partially responded, prompting the later addition of metformin. He reported having labile blood glucose levels with several episodes

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of hypoglycemia on this combination. His family history was significant for T2DM. On examination, his blood pressure was 120/80 mm Hg, pulse 80 beats per min, respiratory rate 16/min, with a body mass index (BMI) of 22.9 kg/m^2. The rest of his physical examination was unremarkable. Laboratory workup revealed HbA1C of 7.1% (normal < 6.5%). With LADA and maturity onset diabetes of the young (MODY) as considerations, C-peptide and glutamic acid decarboxylase 65 (GAD-65) antibody assays were ordered. Presumptive diagnosis of LADA was made with positive C-peptide level (1.10 ng/mL; NR: 0.8 - 3.1) which was later confirmed by positive GAD-65 antibodies (13.1 U/mL; negative is 0 - 5 U/mL). Oral agents, metformin and glipizide were discontinued and he was started on basal and pre-meal insulin treatment.

Discussion

The chronic immune-mediated destruction of islet insulin-secreting β cells, associated with both cellular and humoral immune changes can be detected in the peripheral blood months or even years before the onset of clinical diabetes. In the prediabetic period, metabolic changes like altered glucose tolerance and reduced insulin secretion progress at variable rates and eventually result in clinically manifest diabetes. A fraction of patients with onset of diabetes in adult life but who do not require insulin initially appear to have T2DM. These patients demonstrate the same disease process, autoantibodies to islet cell antigens, low insulin secretion, a higher rate of progression to insulin dependency and similar HLA genetic susceptibility as patients with type 1 diabetes, hence the term LADA.

Most patients are over the age of 30 years at the time of diagnosis with LADA. Since the patients are older at presentation than is typical for those with type 1diabetes and because residual pancreatic insulin production exists, patients with LADA are often labeled as T2DM. LADA shares genetic features of both type 1 (HLA, INS VNTR, and PTPN22) and type 2 (TCF7L2) DM [5].

Because of the clinical presentation, patients may initially be treated with oral hypoglycemic agents especially sulphonylureas and/or biguanides. Following this treatment, there is a characteristic initial response followed by rapid development of refractoriness to oral hypoglycemic agents as the affected patient becomes insulin-requiring soon after diagnosis.

Some clues that point towards LADA are age of onset greater than 25 - 30 years but less than 50 years, BMI < 25 kg/m^2 with low magnitude hyperglycemia, and normal or near-normal C-peptide values. Patients with LADA traditionally respond poorly to oral anti-hypoglycemic agents and often lack family history of T2DM. Assays for autoantibody to GAD-65 (anti-GAD-65 antibody) in patients with recent-onset T2DM are recommended as the initial step in identifying patients with LADA, as this is the most sensitive and specific marker for this subgroup of diabetics [5]. Single antibody positivity and low titer antibodies are markers for LADA associated with the clinical and metabolic phenotype of T2DM patients. HLA typing may help to support with the diagnosis of LADA, and baseline C-peptide evaluation may help assess β-cell function. In addition, the monitoring of C-peptide levels may be helpful with the timing of insulin therapy [5-8].

Our patient demonstrated refractoriness to oral hypoglycemic therapy, a finding seen in patients with LADA. His C-peptide results suggested residual B-cell function at the time of his presentation. Some studies suggest that B-cell failure may take up to 12 years to develop in the setting of LADA [5]. The presence of GAD antibodies, as in our patient, is a strong predictor of future B-cell failure [5, 6].

It should be noted that the presence of obesity does not preclude a diagnosis of LADA [5]. Our patient was obese at the time of initial diagnosis of diabetes, but lost weight in the course of his illness likely as a result of inadequate glycemic control.

With regard to oral hypoglycemic agents, treatment with sulphonylureas is one of the recognized risk factors for progression of B-cell failure, in addition to islet cell antibody (ICA) positivity and obesity [9, 10].

The frequency of LADA among patients presumptively diagnosed as T2DM varies between 6% and 50% in various populations [11-13]. Some studies suggest it may account for about 10% of incident cases in diabetics aged 40 - 75 years [5, 11-13].

In the United Kingdom Prospective Diabetes Study (UKPDS 25), GAD-65 antibodies were positive in 10% of the cohort of > 5,000 patients with T2DM, whereas ICA was positive in 6% of the patients. The prevalence of these antibodies was also found to be higher in younger patients. GAD-65 was positive in 34% and ICA in 21% of patients aged 25 - 34 years. Data from the UKPDS have also shown that in diabetic patients aged between 35 and 45 years, those who tested positive for both GADA and ICAs progressed rapidly toward insulin dependency, usually within 3 years [11-13].

Patients with high GADA titers were younger and had lower BMI, shorter disease durations and lower serum C-peptide levels than the patients with low GADA titers and those who were GADA negative. Testing for anti-GAD in adult-onset non-obese diabetic patients should be routinely done in order to detect latent insulin-dependency at the earliest possible stage, since this assay may assist with the correct classification of disease and the use of appropriate therapy. Interestingly, hypertension, hyperlipidemia, obesity and coronary artery disease (CAD) occur with lower frequency in patients with LADA than in those with T2DM, though micro-vascular complications are comparable [6-8].

In patients with LADA, insulin therapy is highly beneficial as it improves C-peptide secretion (due to improved β-cell function with a higher natural insulin production), reduces HbA1c levels and islet cell autoantibody concentration and also reduces glucose toxicity [5, 10].

As in our patient, a diagnosis of LADA should be considered when a patient presumed to have T2DM is lean, physically active or has recently lost weight unintentionally. Initial management may consist of dietary measures, weight reduction if appropriate, and exercise. Insulin therapy will almost likely be needed in the course of the disease, although this may not be needed for up to 3 - 12 years after diagnosis [5]. Anti-GAD antibodies (or ICA) may help differentiate patients with T2DM from those with LADA [14-16]. Once diagnosed,

insulin therapy should be initiated as early as possible to delay rapid islet cell failure and to prevent further complications. As immune-modulatory therapies that slow or halt the disease process in type 1 diabetes are discovered, testing these therapies in LADA will be essential.

LADA has been described in different clinical contexts in recent times [17-19]. It is reported to be one of the possible causes of refractory hyperglycemia following bariatric surgery [18]. Use of newer diabetes treatments like liraglutide can also precipitate ketoacidosis in patients with LADA who are erroneously diagnosed as T2DM as illustrated by a case report from the UK [19].

Our patient was treated with a regime of mealtime and basal insulin with good clinical response. This case highlights the need for a closer look at the clinical phenotypes of diabetes commonly encountered in the primary care setting, and a high index of clinical suspicion for some of the less common types of diabetes is needed, given the implications. Once identified, early initiation of insulin therapy should be considered, to delay early islet cell failure.

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