Case Report

Type 1 Diabetes (T1D) and Latent Autoimmune Diabetes in Adults (LADA): The Difference Between a Honeymoon and a Holiday

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Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease in which destruction of the insulin-producing β-cells in the pancreatic islets requires regular lifelong insulin replacement therapy, the only lifesaving treatment available at this time. In young persons with a genetic predisposition, it usually manifests after being exposed to environmental triggers. A subtype of autoimmune diabetes mellitus (ADM) that typically occurs in adulthood is often referred to as latent autoimmune diabetes of adults (LADA). LADA is characterized by a milder process of β-cells destruction and less intensive insulin treatment, which may become necessary even many years after diagnosis. Genetic predisposition of T1D carries an increased risk for other autoimmune diseases, such as autoimmune thyroiditis, the most frequently associated condition, and pernicious anaemia (PA), present in approximately 4% of all individuals with T1D. Here, we describe the case of a 90-year-old woman with vitiligo and a mute medical history who was admitted to our University Hospital in Perugia with hyperglycaemia and severe anaemia due to vitamin B12 (VB12) depletion. A short time after setting the beginning treatment with a basal-bolus insulin regimen, her insulin requirement rapidly declined and treatment with sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP4), was started. A complete autoimmunity screening panel showed that GAD65 and intrinsic factor autoantibodies were positive.

1. Introduction

ADM is a chronic autoimmune disease affecting pancreatic insulin-producing β-cells that encompasses a wide spectrum of different clinical presentations. T1D is usually diagnosed at a young age; it manifests with ketoacidosis and requires lifelong insulin replacement therapy while LADA emerges later in life and insulin therapy can be postponed for years after diagnosis.

ADM is frequently accompanied by other autoimmune endocrine and nonendocrine diseases, the latter encompassing the so called “autoimmune polyglandular syndromes (APS),” more common in females. Among these is pernicious anaemia (PA), a form of autoimmune gastritis with impaired VB12 absorption.

In this report, we describe the unusual case of a polyautoimmune syndrome clinically emerging at an old age.

2. Case Presentation

The patient was a 90-year-old woman admitted to our clinical unit at the Perugia University Hospital, Perugia, Italy, for dyspnoea, anorexia, and agitation. Her body mass index was at the lower normal limit, she had a mute medical history, no family history of diabetes mellitus, no history of smoking or other unhealthful habits. Relatives did not report previous episodes of anaemia or bleeding or recent viral infections. She was not on medications except furosemide prescribed a week earlier by the family doctor, due to worsening dyspnoea and peripheral oedema in the lower limbs.

The patient tested negative on the SARS-CoV-2 molecular test performed in the emergency department. Blood tests at admission showed a haemoglobin value of 5.4 g/dL, with a high mean corpuscular volume (MCV) of 109.1 fl,
The patient was discharged with close outpatient monitoring for one month. At the one-month clinical evaluation, glycaemic control was still acceptable without insulin therapy. In order to prevent hypoglycaemic episodes and preserve the remaining β-cells function treatment with daily sitagliptin 100 mg, an oral glucose-lowering drug inhibiting the dipeptidyl peptidase-4 (DPP4) enzyme was started.

The subsequent follow-up visits confirmed the constant fair glycaemic control over time: the blood analysis one year later showed that haemoglobin was 13.7 g/dL, fasting plasma glucose was 92 mg/dL, and glycated haemoglobin was 5.9% (41 mmol/mol). The patient was still on daily sitagliptin 100 mg.

3. Discussion

The pathogenesis of T1D is well-known to involve both genetic and environmental factors [3]. Specific human leucocyte antigen (HLA) haplotypes, such as HLA-DR4-DQ8 and HLA-DR3-DQ2 [4], provide the immunological basis of the development of the disease once the subject has been exposed to external antigens. This exposure induces a T-lymphocyte-mediated reaction against pancreatic β-cells leading to their destruction and consequently to the loss of insulin production.

Shortly after a T1D diagnosis, a period occurs known as “diabetes honeymoon phase,” or remission phase, lasting a variable length of time, usually from weeks to months; nevertheless, there have been some reported cases of this honeymoon lasting for years [5, 6].

The hallmarks of the honeymoon period are low or no insulin requirement together with a fair blood glucose control, with less glucose variability, less risk of hypoglycaemia, and lower overall average blood glucose levels [7]. In this phase, the remaining insulin-producing cells keep on working until they are finally killed off and the honeymoon comes to an end with insulin needs rising again.

In the case of LADA, the destruction of the insulin-producing cells by the self-reactive T lymphocytes proceeds at a slower speed and more mildly. Although questioned by some authors [8, 9], the criteria on which the diagnosis usually rests were proposed by the Immunology of Diabetes Society (IDS) in 2005: (1) onset age greater than 35 years, (2) islet autoantibodies as a marker of the autoimmune process, and (3) insulin independence for at least 6 months after diagnosis [10]. LADA shares genetic susceptibility and clinical phenotype both with T1D and T2D, thus suggesting it is a continuum between the two extremes [11].

Compared to patients with isolated T1D, those with T1D plus autoimmune diseases (AIDs) are older and exhibit a higher female: male ratio; average patient age and age at disease onset are higher in T1D plus AID vs T1D only [12]. Disease risk is associated with organ-specific autoantibodies, which can be used to screen subjects with T1D [13, 14]. Among these diseases, hypothyroidism occurs most frequently while adrenal gland insufficiency occurs the least. LADA has wide genetic overlap with T1D, actually sharing a great risk of other AID. Moreover, the risk seems to be
related to the GAD65 titre displayed by the subject at the moment of diagnosis [15], and, as in T1D, is maximum for hypothyroidism and minimum for adrenal gland insufficiency [15, 16].

In particular, in people with T1D, PA has a mean prevalence of 4.3% vs 0.2% in the general population [17], while no data are reported in the literature about the prevalence of PA in subjects with LADA. PA is marked by the presence of circulating antibodies to intrinsic factor which prevent VB12 absorption leading to a progressive decrease in vitamin storage, which is ten times more common in people with T1D than in nondiabetic persons [18, 19]. VB12 deficiency, in turn, leads to megaloblastic anaemia and neurological symptoms such as peripheral neuropathy and cerebral manifestations (confusion and psychosis) [20].

A Japanese report of people of all ages and both genders with concomitant PA and T1D showed that the subjects were mostly older women (the oldest was 87 years old) who exhibited T1D approximately 10 years prior to PA and had other AID, especially thyroiditis [21]. In the case of our 90-year-old female patient the association of vitiligo, ADM and PA matches the criteria of APS-4.

Differential diagnosis between T1D and LADA can sometimes be presumptive because rather than totally different pathological entities, they represent a seamless continuum. When the patient was initially referred to our clinical unit, we thought she could have T1D due to her phenotype (thin and with vitiligo) and the concomitant acute occurrence of another AID, PA. When her insulin...
hypothesis and fully fulfilled the IDS LADA criteria [10].

improvement in glycaemic control on sitagliptin treatment
insulin secretory capacity is preserved. (ıhe marked im-

needs declined so quickly until the complete withdrawal, we
wondered whether it was a honeymoon phase of T1D or a
LADA, the two autoimmune conditions under which the
insulin secretory capacity is preserved. The marked im-

After carrying out a comprehensive review of the cur-
rently available literature, we found no cases of APS diag-
nosed above 90 years old and only few cases of autoimmune
diabetes emerged in very elderly individuals. Oriol et al. [22]
reported the case of a 93-year-old woman whose diabetes
was undoubtedly T1D as the onset was characterized by
ketoacidosis proven by the presence of high levels of ketones
in the urine sample together with metabolic acidosis.
Moreover, the woman tested positive for more than one
pancreatic islet autoantibody and immediately after the
diagnosis insulin therapy became an irreplaceable treatment.
A case of T1D in a 93-year-old woman with very akin clinical
features has now been reported also by Ahmad et al. [23].
The oldest ultraelderly case of acute-onset autoimmune
diabetes described so far by Yamaguchi et al. is instead of a
96-year-old Japanese woman who presented without
ketoacidosis and in which insulin therapy became pleonastic
few days after the diagnosis despite high anti-GAD antibody
titre. She died few months after the discharge and whether
she was experiencing a honeymoon phase or a LADA was
impossible to ascertain [24].

The paucity of cases reporting newly diagnosed ADM in
the elderly underlines the exceptionality of our case but
could also be a warning of the risk of misclassification of
adult-onset diabetes. Actually, there may be a latent pro-
portion of adult-onset ADM misclassified as T2D due to the
heterogeneous clinical features of LADA. Moreover, as the
human average lifespan is lengthening, acute-onset auto-
immune diabetes at an advanced age may be increasingly
ergeous in the close future.

In accordance with the current literature, our report
demonstrates that a person may be born with a genetic
pattern predisposed to autoimmunity, but this is not enough
to make the disease surface. The time may come, however,
when due to an external trigger such as an infection, the
immune system react and misrecognizes its own genetic
epitopes destroying the cells on which they are expressed.
Contrary to the Japanese report cited above [21], we can see
looking at our patient’s laboratory data from the years before
she came to our attention, VB12 depletion and the pro-
gressive increase in fasting plasma glucose began roughly at
the same time. In 2013, seven years before the admission,
fasting plasma glucose was slightly increased and VB12 was
at the lower limit of normal with a haemoglobin amount
related to the age of the patient, while in 2019, the year before
admission, glycemia was far beyond a normal range and the
VB12 pool was declining, but still no anaemia appeared. As
far as we know, no treatment was initiated to correct both
VB12 depletion and hyperglycaemia.

It is also important to underline that being a genetic
predisposition the sine qua non for AID emergence, there is a
high prevalence of autoimmunity recurrence in offspring. In
fact, both sons of the patient have vitiligo: we invited them to
perform a complete autoimmunity screening panel and to
maintain longitudinal control with regular blood tests.

Data Availability

The data are available in the archives of our hospital.

Conflicts of Interest

The authors declare no conflicts of interest.

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