

OBSERVATIONS

**Pancreas Histology and a Longitudinal Study of Insulin Secretion in a Japanese Patient With Latent Autoimmune Diabetes in Adults**

**P**ositive islet cell-related autoantibody is thought to reflect the process of immune-mediated  $\beta$ -cell damage symbolized by the insulinitis, but there have been few reports on the pancreas histology of latent autoimmune diabetes in adults (LADA). We report a study of pancreas histology and a longitudinal insulin secretion in a LADA patient.

A 50-year-old woman treated with sulfonylurea from the age of 40 years was referred to our hospital in 1999. On the first visit, she was prescribed 5 mg/day glibenclamide. Her BMI was 18.2 kg/m<sup>2</sup>; her maximum BMI at age 40 years, was 26.5 kg/m<sup>2</sup>; her A1C was 7.8%. She was positive for GAD antibody (titer was 20.6 units/ml, normal range <1.5 units/ml) (1) but negative for insulinoma-associated protein 2 (IA2) antibody, zinc transporter 8 antibody, thyroglobulin antibody, and thyroid peroxidase (TPO) antibody. Her fasting serum C-peptide level was 0.66 nmol/l. She possessed a Japanese type 1 diabetes-resistant HLA class II haplotype, *DRB1\*0803-DQB1\*0601*, and neutral *DRB1\*0405-DQB1\*0302* haplotype (1). She initiated insulin treatment to control blood glucose levels. At the age of 54 years, a pancreas biopsy was performed, with written informed consent at the time of laparotomy. At this time, her BMI was 20.6 kg/m<sup>2</sup>, A1C was 8.4%, GAD antibody titer was 23.1 units/ml, and fasting serum C-peptide level was 0.47 nmol/l. Examination by light microscopy revealed normal-shaped islets and exocrine glands. Immunohistochemical examination revealed preserved  $\beta$ - and  $\alpha$ -cell masses. Insulinitis and hyperexpression of

major histocompatibility complex class I or class II molecules (2) were not observed in more than 30 islets that were examined.

At the ages of 54 and 55 years, the patient's GAD65-specific antibody epitopes were analyzed by a radioligand-binding assay using chimeric GAD65/GAD67 constructs (3). Her GAD antibodies recognized both middle and COOH-terminal portions of GAD65 but not GAD67. Intramolecular epitope spreading was not observed.

The patient's GAD antibody titer has gradually been decreasing since the age of 58 years and was 7.0 units/ml in June 2008. IA2 and TPO antibodies have not been detected to date. Fasting and postprandial serum levels of C-peptide have been fairly constant (0.40 and 1.35 nmol/l, respectively, in February 2008) during the observation period.

Shimada et al. (4) reported T-cell insulinitis in a LADA patient positive for both GAD and IA2 antibodies and who had a type 1 diabetes-susceptible HLA class II haplotype. Our case had only GAD antibody, no susceptibility HLA class II, and no insulinitis. We have reported the heterogeneity of Japanese LADA patients, noting that insulin secretion does not necessarily decrease over time and that the additional presence of IA2 or TPO antibodies is related to the  $\beta$ -cell failure (1). In a recent report of adult nondiabetic organ donors with islet cell-related autoantibodies (5), the presence of one or two islet cell-related autoantibodies was not associated with insulinitis.

In conclusion, the process of impaired  $\beta$ -cell function in a subset of LADA patients is different from that occurring in acute-onset type 1 diabetes. The presence or absence of insulinitis is possibly related to the clinical course of LADA, and pancreas biopsy may be useful to predict future  $\beta$ -cell function.

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