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CASE REPORT

# First-onset type 1 diabetes in an elderly woman with multiple islet-associated autoantibodies, and a literature review.

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*Key words:* **type 1 diabetes; elderly; GAD; glutamic acid decarboxylase; IA-2, insulinoma-associated protein 2; multiple islet-associated autoantibodies**

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**Abstract**

An 80-year-old Japanese woman had shown no indication of diabetes but regularly saw a primary-care physician for health management. Six months before her referral to our hospital, her HbA1c was 6.0%. She was referred to us for diabetic ketosis because she was urine ketone body-positive with a blood glucose level of 397 mg/dL and HbA1c of 14.6%. She was diagnosed with type 1 diabetes mellitus (T1DM) with glutamic acid decarboxylase (GAD) antibodies >2,000 U/mL (by ELISA) and IA-2 antibodies >30 U/mL. Insulin injections were introduced, and she was discharged. Laboratory tests during her hospitalization were negative for thyroid antibodies (TgAb, TPOAb). Elderly individuals with first-onset T1DM who are positive for IA-2 antibody are rare, and multiple-positive cases of pancreatic islet-associated autoantibodies are particularly rare. IA-2 antibodies have an approx. 60% positive rate in acute-onset T1DM, but they are more likely to be positive in children and adolescents and are known to turn negative earlier than anti-GAD antibodies. Although a large amount of insulin is needed in general in such cases, our patient was successfully treated with a small amount of insulin. IA-2 antibody has been reported to be positive even in GAD antibody-negative individuals. In some cases, IA-2 antibody and other antibodies are positive even in elderly-onset diabetes, and this contributes to the diagnosis of T1DM.

**Abbreviations:**

| | |
|---|---|
| GAD | - glutamic acid decarboxylase |
| IA-2 | - insulinoma-associated protein 2 |
| IAA | - insulin autoantibodies |
| ICA | - islet cell antibody |
| IDDM | - insulin dependent diabetes mellitus |
| TPO | - thyroid peroxidase |
| TSH | - thyroid-stimulating hormone |
| ZnT8A | - zinc transporter 8. |

## INTRODUCTION

Elevated concentrations of autoantibodies against pancreatic β cells are valuable for the diagnosis of type 1 diabetes mellitus (T1DM). The antigens for these autoantibodies are glutamic acid decarboxylase (GAD), insulinoma-associated protein 2 (IA-2), insulin autoantibodies (IAA), and zinc transporter 8 (ZnT8A) (Knip *et al.* 2016). IA-2 antibody is a diabetes-specific islet autoantigen

**Tab. 1.** The patient's laboratory and urinalysis data

| Indicators | Results | References |
|---|---|---|
| WBC, /μL | 5100 | 3300-8600 |
| RBC, /μL | $436\times10^4$ | $386\text{-}492\times10^4$ |
| Hb, g/dL | 13.5 | 11.6-14.8 |
| Plt, /μL | $29.2\times10^4$ | $15.8\text{-}34.8\times10^4$ |
| ALB, g/dL | 4.3 | 3.9-5.2 |
| BUN, mg/dL | 10.0 | 8-20 |
| Cr, mg/dL | 0.50 | 0.4-0.8 |
| UA, mg/dL | 2.8 | 3-7 |
| Na, mmol/L | 134 | 136-145 |
| K, mmol/L | 4.3 | 3.6-4.8 |
| Cl, mmol/L | 95 | 99-107 |
| T-Bil, mg/dL | 0.7 | 0.4-1.3 |
| AST, IU/L | 52 | 10-35 |
| ALT, IU/L | 52 | 5-40 |
| LDH, IU/L | 335 | 120-220 |
| ALP, U/L | 151 | 100-320 |
| γ-GTP, U/L | 137 | 5-40 |
| CRP, mg/dL | 0.30 | 0-0.35 |
| Plasma glucose, mg/dL | 271 | 80-110 |
| C-peptide, ng/mL | 0.51 | 0.8-5.2 |
| HbA1c, % | 14.7 | 4.3-5.9 |
| GA, % | 49.0 | 12-16.4 |
| HDL, mg/dL | 105 | 40-100 |
| LDL, mg/dL | 171 | 60-139 |
| TG, ng/mL | 41 | 30-150 |
| CA19-9, U/mL | <0.5 | <38 |
| CEA, ng/mL | 2.2 | <6 |
| FT4, μU/mL | 0.99 | 0.7-1.8 |
| TSH, μU/mL | 1.10 | 0.61-4.23 |
| Venous blood: | | |
| pH | 7.387 | 7.350-7.4 |
| $PaCO_2$, mmHg | 42.5 | |
| $PaO_2$, mmol/L | 34.3 | |
| $HCO_3$, mmol/L | 24.9 | |
| BE, mmol/L | −0.2 | |
| Anion gap | 20.1 | |
| GAD Ab, U/mL* | >2,000 | negative |
| IA-2 Ab, U/mL | >30 | negative |
| ICA Ab, JDF units | 640 | negative |
| ZnT8 Ab, U/mL | 1110 | negative |
| Insulin Ab, U/mL | <0.4 | <0.4 |
| Anti-TPO Ab, IU/mL | <9 | <16 |
| Anti-TG Ab, IU/mL | 10 | <28 |
| HLA DNA | | |
| DRB1 | 09:01 | |
| DQB1 | 03:03 | |
| **Urinalysis** | | |
| Glucose | 4+ | |
| Protein | – | |
| Bilirubin | – | |
| Blood | – | |
| Ketones | 2+ | |

*by ELISA

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Plt, platelet; ALB, albumin; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; Na, sodium; K, potassium; Cl, chlorine; T-Bil, total bilirubin; AST, L-aspartate; ALT, L-alanine; ALP, alkaline phosphatase; γGTP, γ-glutamyl transferase; CRP, C-reactive protein; HbA1c, hemoglobin A1c; GA, glycoalbumin; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol; TG, triglyceride; CA19-9, carbohydrate antigen 19-9, CEA, carcinoembryonic antigen; FT4, free thyroxine; TSH, thyroid stimulating hormone; $PaCO_2$, venous carbon dioxide tension; $PaO_2$, arterial oxygen tension; $HCO_3$, bicarbonate concentration; BE, base excess; GAD Ab, anti-glutamic acid decarboxylase antibody; IA-2, anti-insulinoma associated antigen-2; ICA, anti-cytoplasmic islet cell antibody; ZnT8, zinc transporter 8; Insulin Ab, anti-insulin antibody; Anti-TPO Ab, anit-thyroid peroxidase antibody; Anti-TG Ab, anti-thyroglobulin antibody; HLA DNA, human leukocyte antigen deoxyribonucleic acid; DRB1, human leukocyte antigen DRB1; DQB1, human leukocyte antigen DQB1

related to protein tyrosine phosphatases (Rabin *et al.* 1994). The prevalence of IA-2 is reported to be higher in younger patients (≤15 years old) with recent-onset insulin-dependent diabetes mellitus (IDDM) (64/113; 57%) compared to patients >15 years old (11/25; 44%) (Masuda *et al.* 2000). We describe the unusual case of an elderly patient with T1DM and a high IA-2 antibody level.

## CASE REPORT

An 80-year-old Japanese woman was referred to our hospital due to weight loss. She had shown no indication of diabetes, and she continued to visit a primary-care physician regularly for health management. At her presentation, the examination revealed a blood glucose level at 397 mg/dL and HbA1c at 14.6%, and urine ketone bodies were detected. She was admitted to our hospital for diabetic ketosis. Her past medical

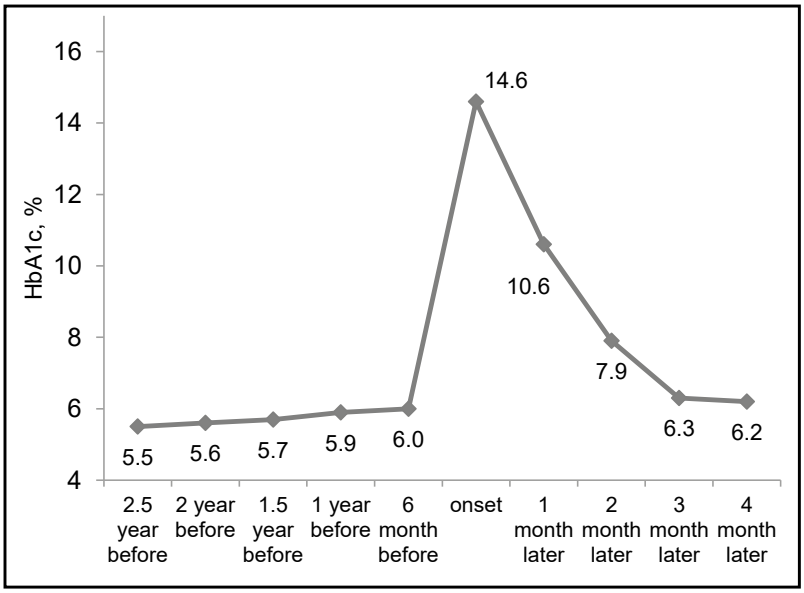


**Figure 1.** The patient's HbA1c values before and after the onset of type 1 diabetes

history was significant for dyslipidemia. She had no history of alcohol use, smoking, allergy, or obesity, and she had no family history of diabetes mellitus. She had been treated with simvastatin. She consumed no snacks or soft drinks. Her exercise history was playing tennis 3×/week.

Her common vital signs were as follows: mean arterial blood pressure, 131/79 mmHg; pulse rate, 73 beats/minute; body temperature, 36.9°C; height, 1.54 m; and body weight, 38.6 kg. Her body mass index was 16.2 kg/m$^2$. Her physical examination showed no bulbar conjunctival yellowing, no palpebral conjunctival anemia, no cervical lymphadenopathy, no thyroid swelling, no tenderness, pure heart sound, clear respiratory sound bilaterally; flat soft, normal intestinal peristaltic sound, and no tenderness in the abdomen. A neurological examination showed that the patient's lower extremity vibratory sensation was left 12 sec/right 12 sec, and the patellar tendon reflex and Achilles tendon reflex were normal.

Laboratory findings on admission are provided in Table 1. The urinalysis revealed glucose at 4+, ketouremia at 2+, and a decreased urinary C-peptide level. Serum chemistry values were as follows: glucose, 271 mg/dL (normal range: 73–109 mg/dL); C-peptide, 0.51 ng/mL (normal range: 0.8–5.2 ng/mL); glycosylated hemoglobin, 14.7% (normal range: 4%–6.5%); glycoalbumin, 49.0% (normal range: 12%–16.4%); GAD antibody, >2000 U/mL (normal: <5.0 U/mL); IA-2 antibody, >30 U/mL (normal: <0.6 U/mL); ICA antibody, 640 JDF units (normal: <1.25 JDF units); and ZnT8 antibody, 1110 U/mL (normal: <15.0 U/mL). Insulin antibody, anti-TPO antibody, and anti-thyroglobulin antibody were all negative. The patient was considered susceptible to T1DM, as her HLA DNA allele was DRB1 09:01-DQB1 03:03. Abdominal ultrasonography and carotid artery ultrasound showed no abnormalities.

The patient's HbA1c was between 5.5% and 6.0% before the onset of T1DM; it then worsened to 14.6%. With frequent injections of insulin for acute-onset T1DM, her HbA1c improved to 6.2% (Figure 1). The total insulin doses were reduced from 17 units/day at the beginning to the final dose 11.5 units/day (insulin lispro 4-1.5-2 IU before meals and insulin degludec 4 IU at lunch).

## DISCUSSION

As a characteristic of various pancreatic islet-related autoantibodies, anti-insulin antibody is present in 18% of untreated cases of T1DM (Palmer *et al.* 1983). It was reported that the presence of insulin autoantibodies in patients with ICA was associated with greater deficiencies of insulin secretion than patients lacking insulin autoantibodies. (Atkinson *et al.* 1986). In our patient, the insulin autoantibody result was negative. The rate of GAD antibody positivity in Japanese patients with acute-onset T1DM is as high as 70%–80% (Kawasaki *et al.* 2011). Interestingly, our patient's GAD antibody level was high but she didn't have autoimmune thyroid disease, although it is reported that high levels of GAD antibodies were present in IDDM patients with autoimmune thyroid disease (Kawasaki *et al.* 1994).

IA-2 antibody has a positive rate of approx. 60% in acute-onset T1DM (Sera *et al.* 1999), but it is more likely to be positive in children and adolescents (Masuda *et al.* 2000). It was reported that IA-2 antibody often turns negative at an earlier timepoint compared to GAD antibody in children and adolescents but sometimes remains positive in adults for a period of a few years (Nakamoto *et al.* 2000). Although the amount of insulin required in such cases is often large (Ota *et al.* 2003), our patient was successfully treated with a small amount of insulin.

**Tab. 2.** Patients who were positive for multiple antibodies in Japan (n=22). F: female, M: male.

| No. | First author, year | Age/ sex | GAD | IA-2 | IIA/ ICA | ZnT8 | TPO | TG | Type | HLA |
|---|---|---|---|---|---|---|---|---|---|---|
| Present patient | | 80 F | ++ | ++ | –/– | + | – | – | Acute | Susceptible |
| 1 | Takahashi 2018 | 94 F | ++ | + | –/– | + | – | – | Acute | Resistant |
| 2 | Yamazaki 2016 | 90 M | – | + | –/– | + | | | Slow | Susceptible |
| 3 | Yamamoto 2005 | 86 F | + | + | | | | | Slow | Susceptible |
| 4 | Fujita 2000 | 80 F | + | – | /+ | | – | + | Slow | Susceptible |
| 5 | Tsuji 2010 | 80 M | ++ | ++ | –/– | | + | | Acute | Susceptible |
| 6 | Morimoto 2015 | 79 F | ++ | ++ | | | + | + | Acute | Susceptible |
| 7 | Kodama 2000 | 78 M | + | + | | | – | – | Slow | |
| 8 | Watanabe 2011 | 72 F | + | + | –/– | | – | – | Acute | Susceptible |
| 9 | Yajima 2016 | 72 F | + | + | | | | | Acute | Susceptible |
| 10 | Kubo 2013 | 71 M | ++ | ++ | | | – | – | Slow | Susceptible |
| 11 | Tachikawa 2011 | 71 M | ++ | – | –/+ | | – | – | Acute | Resistant |
| 12 | Nakagiri 2013 | 70 F | + | + | +/+ | | + | + | Acute | Susceptible |
| 13 | Aikawa 2020 | 70 F | – | + | +/+ | | – | + | Acute | |
| 14 | Watanabe 2020 | 69 F | ++ | + | –/– | – | + | + | Slow | Susceptible |
| 15 | Naito 2013 | 68 F | + | + | /– | | + | – | Slow | Susceptible |
| 17 | Takahashi 2008 | 67 F | ++ | ++ | | | | | Slow | |
| 18 | Go 2009 | 65 F | + | + | +/+ | | – | – | Slow | Susceptible |
| 19 | Iijima 2018 | 65 F | + | ++ | /– | | + | + | Acute | Susceptible |
| 20 | Takeshima 2012 | 64 F | + | + | –/+ | | – | – | Slow | Susceptible |
| 21 | Obata 2008 | 63 F | + | ++ | –/+ | | + | + | Slow | Susceptible |
| 22 | Yasui 2014 | 61 F | + | + | | + | + | + | Acute | Susceptible |

F: female, M: male.

ZnT8 antibody is a relatively newly identified antibody, first described in 2007 (Wenzlau *et al.* 2007). It is positive in approx. 60% of Caucasian patients with T1DM (Wenzlau *et al.* 2007). The positive rate of ZnT8 antibody is high in children and adolescents (Wenzlau *et al.* 2007). Approximately 4% of patients with T1DM are positive for ZnT8 while other antibodies are negative (Wenzlau *et al.* 2007). Based on the above reports, it is apparent that positive cases of IA-2 and ZnT8 antibodies are common in children, but they are thought to be rare in the elderly. It was also reported that 22 patients with T1DM in Japan were positive for multiple antibodies (Table 2). In some of those 22 patients, IA-2 antibody was positive even when GAD antibody was negative. Our present patient's case demonstrates that even among individuals with diabetes that develops at an advanced age, there are cases in which IA-2 antibody and other antibodies are positive, which may contribute to the diagnosis of T1DM.

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