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CASE REPORT

New-onset type 1 diabetes and Graves' disease after antiretroviral therapy in a patient with human immunodeficiency virus infection

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ABSTRACT

Patients with human immunodeficiency virus (HIV) infection receiving antiretroviral therapy can develop autoimmune diseases, referred to as immune-inflammatory reconstitution syndrome. Nevertheless, only a few reports on the onset of type 1 diabetes as immune-inflammatory reconstitution syndrome are available. A 40-year-old Japanese man with HIV infection was initiated with antiretroviral therapy at the age of 29 years. He developed Graves' disease at 35 years and diabetes, with a hemoglobin A1c of 6.5%, and maintained insulin secretion at 38 years. His antiglutamic acid decarboxylase antibody level was >2,000 U/mL, and he was diagnosed with slowly progressive type 1 diabetes. At the age of 40 years, he was admitted to our hospital with diabetic ketosis. We retrospectively assayed his stored plasma samples for thyroid-stimulating hormone receptor antibody and antiglutamic acid decarboxylase antibody, which showed positive conversion after initiating antiretroviral therapy, suggesting that Graves' disease and type 1 diabetes developed as a probable result of immune-inflammatory reconstitution syndrome.

INTRODUCTION

Human immunodeficiency virus (HIV) causes immunodeficiency due to a high HIV plasma viral load (pVL) that attacks $CD4^+$ T cells (CD4), eventually leading to decreased CD4 counts and hence, immunodeficiency. Initiation of antiretroviral therapy (ART) reduces pVL and causes a significant increase in CD4 counts, leading to recovery of the immune system. During this immune restoration, a minority of patients experience a paradoxical clinical decline. This phenomenon occurs by virtue of restoration of the capacity to mount an inflammatory response against both infectious and non-infectious antigens, hence the term "immune reconstitution inflammatory syndrome" (IRIS).[1] This might be viewed as a result of organ-specific autoimmunity during the late period of CD4 recovery.[2]

Regarding the association between HIV and diabetes, there are only a few reports on type 1 diabetes as a result of IRIS.[3–6] We recently experienced a case which both Graves' disease (GD) and type 1 diabetes developed after ART initiation, and henceforth, describe the case as a possible manifestation of IRIS.

CASE REPORT

A 40-year-old Japanese man was admitted to National Center for Global Health and Medicine Hospital, Tokyo, Japan, for diabetic ketosis and hyperthyroidism. At the age of 29 years, he was diagnosed with HIV and acquired immunodeficiency syndrome, and ART was initiated. However, he dropped out of the therapy soon after, until at the age of 32 years, when he was reassessed and resumed ART. Three years later, at the age of 35 years, he developed GD, and thiamazole was started. As part of the routine laboratory follow ups, his hemoglobin A1c (HbA1c) levels were maintained at 5.7–6.0%. In his subsequent follow ups, his HbA1c reached 6.6% at the age of 38 years, and the antiglutamic acid decarboxylase antibody (GAD-Ab) was strongly positive. Nevertheless, his insulin secretion was maintained. Three months before this hospitalization, his HbA1c level deteriorated to 9.8%, and hence treatment with vildagliptin 100 mg per day was initiated. However, he discontinued the treatment, except for ART, due to business reasons. He visited

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Table 1 | Patient and laboratory data characteristics on admission

Clinical characteristics	
Age (years)	40
Sex	Male
Retinopathy	NDR
Smoking	Current smoker
Drinking	Non-drinker
Family history of diabetes	None
Height (cm)	169
Weight (kg)	50.7
Body mass index (kg/m^2)	17.6
Laboratory data	
WBC (/μL)	5.26 × 10^3
Neutro (%)	48.7
CD4 (/μL)	291
CD8 (/μL)	1723
Hemoglobin (g/dL)	15.1
Albumin (g/dL)	4.1
Triglyceride (mmol/L)	176
HDL cholesterol (mmol/L)	31
LDL cholesterol (mmol/L)	124
AST (U/L)	13
ALT (U/L)	20
γ-GTP (U/L)	62
eGFR (mL/min/1.73 m^2)	165.2
C-reactive protein (mg/dL)	0.07
Total ketone body (μmol/L)	5,096
Acetoacetic acid (μmol/L)	1,654
Beta-hydroxybutyrate (μmol/L)	3,442
Diabetes	
Glucose (mmol/L)	37.3
HbA1c (%)	13.9
HbA1c (mmol/mol)	128
IRI (μU/mL)	4.1
Fasting plasma CPR (ng/mL)	1.03
ΔCPR (ng/mL) (glucagon stimulated test)[†]	0.18
Pre-load CPR (ng/mL)	0.18
Pre-load glucose (mnol/L)	4.5
Post-load CPR (ng/mL)	0.36
Post-load glucose (mnol/L)	5.4
Urinary CPR (μg/day)	23
Urinary ACR (mg/gCr)	2.81
GAD-Ab (U/mL)	>2000
IA-2-Ab (U/mL)	<0.4
ZnT8-Ab (U/mL)	<10
Thyroid	
TSH (μU/mL)	<0.005
FT4 (ng/dL)	>7.77
FT3 (pg/mL)	18.48
TRAb (IU/L)	28.1
TPO-Ab (IU/mL)	67.1
Tg-Ab (IU/mL)	10.2
HLA typing/genotyping	
A 11/24	
B 54/67	
*DQB1*04:01/05:02*	
*DRB1*04:05/16:02*	

The name of the kits for measuring autoantibodies were as follows: glutamic acid decarboxylase antibody (GAD-Ab): GADAb ELISA COSMIC (reference range: <5.0 U/mL), anti-insulinoma-associated antigen-2 antibody (IA-2-Ab): IA-2Ab RIA COSMIC (reference range: <0.4 U/mL), anti-zinc transporter-8 antibody (ZnT8-Ab): RSR ZnT8 ELISA Kit (reference range: <10 U/mL). ACR, albumin-to-creatinine ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD4, CD4$^+$ T lymphocyte; CD8, CD8$^+$ T lymphocyte; CPR, C-peptide immunoreactivity; eGFR, estimated glomerular filtration rate; FT3, free thyroxine 3; FT4, free thyroxine 4; GAD-Ab, glutamic acid decarboxylase antibody; GTP, glutamyl transpeptidase; HDL, high-density lipoprotein; HLA, human leukocyte antigen; IA-2-Ab, anti-insulinoma-associated antigen-2 antibody; IRI, immunoreactive insulin; LDL, low-density lipoprotein; NDR, nondiabetic retinopathy; Neutro, neutrophil; Tg-Ab, thyroglobulin antibody; TPO-Ab, antithyroid peroxidase antibody; TRAb, thyroid-stimulating hormone receptor antibody; TSH, thyroid-stimulating hormone; WBC, white blood cell; ZnT8-Ab, anti-zinc transporter-8 antibody. [†]A glucagon test was carried out on Day 15.

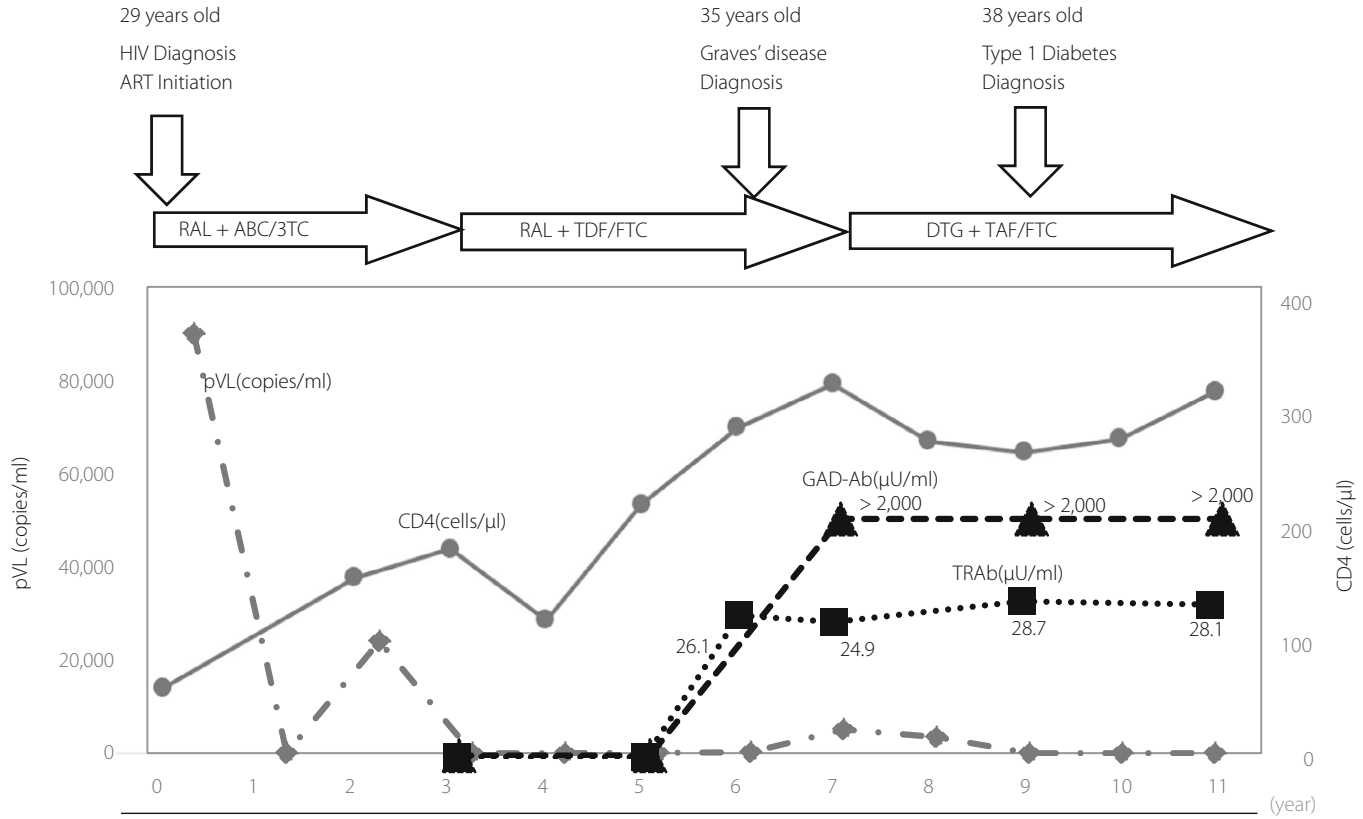
the hospital complaining of weight loss, polydipsia, polyuria and fatigue. Consecutively, the patient's HbA1c level had further increased to 13.9%, and symptoms of ketosis were also observed. Additionally, GD had worsened due to negligence of medication intake, and he was admitted for further assessment and treatment. Table 1 shows the background information and admission laboratories. Ketosis was presumed due to discontinuation of antidiabetic medication and deteriorated endogenous insulin secretion. Oral thiamazole and potassium iodide was started for thyrotoxicosis, and the thyroid hormone levels decreased over time. Furthermore, intensive insulin therapy was initiated for his hyperglycemia. Glycemic control gradually improved and the patient was discharged 13 days after admission.

Analysis of consecutively preserved sera of the case showed that the patient tested positive for thyroid-stimulating hormone receptor antibody and GAD-Ab between the recovery of CD4 and GD and diabetes diagnosis, suggesting that the autoimmune response of the HIV treatment process might be involved in the development of these two diseases (Figure 1). Human leukocyte antigen genotyping showed that the patient had *DQB1*04:01* and *DRB1*04:05*, which constitute susceptibility to type 1 diabetes in the Japanese population.

DISCUSSION

In the present case, emergences of autoantibodies – thyroid-stimulating hormone receptor antibody and GAD-Ab – coincided with the suppression of pVL and significant increases in CD4, and thus we deemed this case to be one of the manifestations of IRIS.

ART improves immunocompetence by decreasing pVL, thereby restoring immune functions, such as those of monocytes, macrophages and natural killer cells, and increasing the number of CD4. Alternatively, the regulatory T-cell activity



CD8 (cells/μl)	1,977	891	2,087	3,171	2,214	2,462	2,259	1,778	1,723
Fasting plasma CPR (ng/ml)							2.97	1.48	1.03
Fasting plasma glucose (mmmol/l)				6.1	5.8	6.5	6.2	6.3	37.3

Figure 1 | Clinical course of the patient before the diagnosis of Graves' disease and type 1 diabetes. $CD4^+$ T cells (CD4) and plasma viral load (pVL), thyroid-stimulating hormone receptor antibody (TRAb), and antiglutamic acid decarboxylase antibody (GAD-Ab) after antiretroviral therapy initiation. ABC/3TC, abacavir/lamivudine; CPR, C-peptide immunoreactivity; DTG, dolutegravir; RAL, raltegravir; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

remains low, which can lead to an excessive immune response and trigger IRIS.[7] Patients with IRIS have lower CD4 counts and higher pVL on ART initiation than those without IRIS (particularly, in patients with a CD4 count of <50/μL and pVL of >100,000 copies/mL before ART initiation).[7] Both low initial CD4 counts, as well as high pVL, were observed in the present case.

There is a consensus that GD is an IRIS, and the onset of the disease is commonly at 12–36 months after ART initiation.[8] GD develops presumably due to the following mechanisms: IRIS is contemplated to have two phases, with an initial increase in memory T cells, followed by an increase in naive T cells. Self-responsive clones might emerge among naive T cells that increase later, thereby increasing the risk of developing autoimmune diseases.[9]

Although the animal model pathophysiology also suggests a correlation between lymphopenia and type 1 diabetes[10] occurrence, the inclusion of type 1 diabetes's as a part of IRIS is still considered controversial. There have been eight cases reported so far (Table 2 and Table S1)[3–6] on this. Commonly, it has a slow progression and a high prevalence among Japanese people, and the duration to the onset of diabetes is 10–264 months.[3,4] Five patients had a positive GAD-Ab 2–50 months before they needed intensive insulin therapy, indicating that GAD-Ab testing during diabetes diagnosis after ART initiation might be significant in predicting a decrease in the endogenous insulin secretion.

The analysis of human leukocyte antigen genotyping showed susceptibility to type 1 diabetes and type 3 autoimmune polyendocrine syndrome. Although we did not investigate the

Table 2 | Characteristics of other patients and laboratory findings on the diagnosis of type 1 diabetes

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Current case
Age (years)	30	31	68	8	40	38	68	27	40
Sex	Male	Male	Female	Female	Male	Male	Male	Male	Male
Race/ethnicity	Japanese	Japanese	Japanese	Hispanic	Japanese	Japanese	African American	Unidentified	Japanese
Duration of HIV infection (months)	132	204	60	90	28	76	360	120	108
Duration of the tolerated ART (months)	18	10	55	80	28	76	264	60	75
CD4 count (cells/μL)	311	172	316	Unknown	Unknown	628	772	950	291
CD4 count at nadir (cells/μL)	12	14	19	Unknown	Unknown	34	2	Unknown	52
Subtype of type 1 diabetes	Slowly progressive	Slowly progressive	Slowly progressive	Slowly progressive	Acute onset	Acute onset	Slowly progressive	Unknown	Slowly progressive
Interval from GAD-Ab positivity to progressive worsening of glycemic control[†] (months)	12	2	17	Unknown	Unknown	50	Unknown	Unknown	48
Casual plasma glucose (mmol/L)	26.6	9.2	8.1	19.4	Unknown	13.7	Unknown	15	8.6
HbA1c (%)	10.8	10.9	12.2	7.5	12.5	6.5	9.4	7.2	6.6
HbA1c (mmol/mol)	94	95	109	58	113	47	79	55	48
GAD-Ab (U/mL)	606	26,000	1,023	4.4	34.8	1,600	>250	>2000	>2000
TRAb (IU/L)	12.6	<1.0	<1.0[‡]	–	Unknown	14.4%[§]	Unknown	22.87	28.7
Graves' disease	–	–	+	–	Unknown	+	Unknown	+	+
HLA genotype	*DRB1*04:05–DQB1*04:01 DRB1*09:01–DQB1*03:03*	*DRB1*08:03–DQB1*06:01 DRB1*09:01–DQB1*03:03*	*DRB1*04:03–DQB1*03:02 DRB1*04:06–DQB1*03:02*	*DRB1*04:05 DRB1*04:01*	*DRB1*09:01–DQB1*03:03*	*DRB1*12:01–DQB1*03:01 DRB1*14:05–DQB1*03:03*	Unknown	Unknown	*DQB1*04:01 DQB1*05:02 DRB1*04:05 DRB1*16:02*

"Antiretroviral therapy" and "diabetes" were used to search in PubMed and Journal of Health Case and Society (Japanese) to find case reports that corresponded to this case series. ART, antiretroviral therapy; CD4, $CD4^+$ T lymphocyte; GAD-Ab, glutamic acid decarboxylase antibody. [†]Test results were described only the patients who had stored serum samples. [‡]The thyroid-stimulating hormone receptor antibody level became positive after the autoimmune diabetes diagnosis. [§]Thyroid-stimulating hormone receptor antibody first generation (binding inhabitation rate).

combination of a haplotype set, it might have influenced the development of these diseases in the present case.

To conclude, some HIV-infected patients develop type 1 diabetes after immune restoration caused by ART. Hence, these immunological studies might aid in understanding the mechanisms of type 1 diabetes in general.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: The authors obtained written consent from the patient to present this case.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Case report references.