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Case Report

AUTOIMMUNE DIABETES IN A PATIENT WITH HUMAN IMMUNODEFICIENCY VIRUS ON ANTI-RETROVIRAL THERAPY WITH LITERATURE REVIEW

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ABSTRACT

Objective: Diabetes that develops in human immunodeficiency virus-infected individuals is typically classified as type 2 diabetes mellitus. Although less commonly reported, it has been shown that autoimmune diabetes can also develop in this population.

Methods: We present a case of a patient found to have autoimmune diabetes following initiation of anti-retroviral therapy.

Results: A 68-year-old, African American man with human immunodeficiency virus had a nadir CD4 count of 2 cells/μL, which improved with anti-retroviral therapy. He was subsequently diagnosed with type 2 diabetes mellitus but developed worsening glycemic control. Further investigation demonstrated an elevated glutamic acid decarboxylase antibody level >250 IU/mL and a declining C peptide level from 1.82 ng/mL to 0.56 ng/mL. He was ultimately diagnosed with autoimmune diabetes that was treated with insulin glargine and insulin aspart with improvement in his glycemic control.

Conclusion: Autoimmune diabetes in this case was attributed to immune reconstitution after anti-retroviral therapy led to recovery from a significantly low CD4 count. While this phenomenon has been described in previous case reports, our case was unique in that autoimmune diabetes affected an older African American man, a different demographic than previously reported. Although the true mechanism of this association remains unknown, the recognition of autoimmune diabetes is crucial as it greatly impacts diabetes management. **(AACE Clinical Case Rep. 2020;6:e201-e206)**

Abbreviations:
AIDS = acquired immunodeficiency syndrome; **ART** = anti-retroviral therapy; **BMI** = body mass index; **DKA** = diabetic ketoacidosis; **GAD** = glutamic acid decarboxylase; **HIV** = human immunodeficiency virus; **IDDM** = insulin-dependent diabetes mellitus; **IRIS** = immune reconstitution inflammatory syndrome; **LADA** = latent autoimmune diabetes in the adult; **T1DM** = type 1 diabetes mellitus; **T2DM** = type 2 diabetes mellitus

INTRODUCTION

Diabetes occurs in approximately 2 to 14% of individuals with human immunodeficiency virus (HIV) (1). The risk is 2 times higher in adults aged 50 to 64 years and 3 times higher for those 65 and older (2). The phenotype is often similar to type 2 diabetes mellitus (T2DM) with many of the traditional risk factors of age, genetic predisposition, and elevated body mass index (BMI). Additional risk factors include anti-retroviral therapy (ART), particularly protease inhibitors and nucleoside reverse transcriptase inhibitors, which can induce insulin resistance and contribute to lipodystrophy, further reducing insulin sensitivity (3). Hepatitis C co-infection may also contribute to diabe-

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tes (1,3). Autoimmune diabetes can affect patients with HIV but is a less commonly reported etiology of diabetes. Although the exact mechanism is unknown, ART initiation and ultimately immune reconstitution may play a role (4). The following case presentation describes a patient with HIV on ART who developed autoimmune diabetes.

CASE REPORT

A 68-year-old, African American man was diagnosed with HIV 30 years prior to presenting to the clinic with diabetes. His history was complicated by cytomegalovirus retinitis and his nadir CD4 count was 2 cells/μL (reference range is 297 to 1,551 cells/μL), which improved over time to 772 cells/μL on ART (Table 1).

Less than 10 years after starting ART, T2DM was diagnosed. His father had diabetes of unknown etiology. His BMI was 22.4 kg/m^2 and there was no history of pancreatitis. Oral glycemic medications were started at diagnosis, and insulin was added to his regimen 13 years after his initial diagnosis. He was transitioned to insulin monotherapy due to renal dysfunction. His hemoglobin A_{1c} was 9.0% (75 mmol/mol) and diabetes was complicated by nephropathy with a creatinine of 3.04 mg/dL (reference range is 0.66 to 1.28 mg/dL).

Eighteen years after his initial diabetes diagnosis, he was referred to a diabetes clinic while on insulin glargine 10 units every morning and 20 units nightly (total daily dose of 30 units). Saxagliptin was added to his regimen without improvement in glycemic control. Since he reported compliance with diabetes medications and monitoring of his diet and activity levels, additional workup was conducted. This evaluation revealed elevated glutamic acid decarboxylase (GAD) antibody >250 IU/mL (reference range is <5 IU/mL) and C peptide of 1.82 ng/mL (reference range is 0.80 to 3.85 ng/mL) with simultaneous serum glucose of 181 mg/dL (reference range is 70 to 110 mg/dL).

The elevated GAD antibody was consistent with autoimmune diabetes. Immune reconstitution was considered as the potential etiology given the significantly low nadir CD4 count, which improved over time. Insulin glargine was continued, insulin aspart was added (total daily dose of 28 units), and saxagliptin was discontinued. Five months later, his C peptide declined to 0.56 ng/mL with simultaneous serum glucose of 133 mg/dL (Fig. 1). Despite basal-bolus insulin, his hemoglobin A_{1c} rose to 12% (108 mmol/mol) due to missed insulin aspart doses, but improved to 10.4% with modifications and ultimately improved to 6.6% (49 mmol/mol).

DISCUSSION

We report a case of an African American man with HIV who developed autoimmune diabetes, attributed to immune reconstitution. A literature review was conducted to identify prior case reports. PubMed was searched using the following terms: HIV type 1 diabetes; AIDS type 1 diabetes; antiretroviral type 1 diabetes; antiretroviral autoimmune diabetes; HIV autoimmune diabetes; AIDS autoimmune diabetes. To be eligible, studies had to be case reports of autoimmune diabetes or insulin-dependent diabetes mellitus (IDDM) or diabetic ketoacidosis (DKA) in humans with HIV or acquired immunodeficiency syndrome (AIDS), published through July 19, 2019 in English. Both authors independently reviewed the studies to confirm their eligibility. Data was extracted with no masking to author list or journal. Reference lists were reviewed and cited reference searches for included manuscripts were conducted.

Of 316 articles found, 313 were excluded as they were not case reports of autoimmune diabetes, IDDM, or DKA diagnosed after ART initiation. We identified 6 antibody-positive autoimmune diabetes cases (4,5,7,8) and 7 IDDM or DKA cases (6,9-14) (Tables 2 and 3). Of the 6 antibody-positive autoimmune diabetes cases (4,5,7,8), 4 were

Table 1
Current Case

Age; sex; ethnicity	BMI (kg/m^2)	FH of DM	GAD (IU/mL); C peptide (ng/mL)	HIV history		At autoimmune DM diagnosis		Comorbidities
				HIV duration (years)	CD4 nadir (cells/μL); concurrent VL (copies/mL)	CD4 (cells/μL); VL (copies/mL)	ART; duration of use	
68; M; AA	22.4	+	>250; 0.56	30	2; unknown	772; undetectable	lamivudine abacavir dolutegravir; 22 years intermittently	CMV retinitis, CKD, HTN

Abbreviations: + = positive; AA = African American; ART = anti-retroviral; BMI = body mass index; CKD = chronic kidney disease; CMV = cytomegalovirus; DM = diabetes mellitus; FH = family history; GAD = glutamic acid decarboxylase; HTN = hypertension; M = male; VL = viral load.

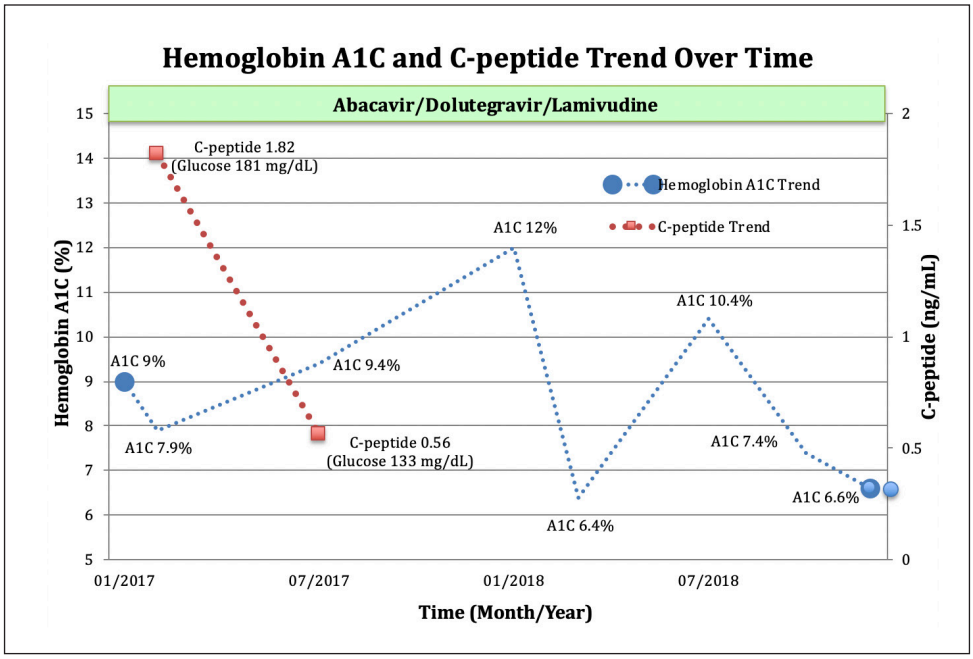

Fig. 1. The patient's change in hemoglobin A_{1c} and C peptide over time.

potentially related to immune reconstitution (4,7). Two were potentially related to other factors, as Bergman et al (8) reported perinatally-acquired HIV with a consistently normal CD4 count and Hughes et al (5) reported autoimmune diabetes after nivolumab treatment. In other reports, Japanese individuals were potentially affected by immune reconstitution with a low nadir CD4 of 12 to 19 cells/μL in one report (4) and <400 cells/μL in another report (7). In both cases, CD4 counts had increased above 100 cells/μL at autoimmune diabetes diagnosis.

Similarly, our patient's nadir CD4 count was 2 cells/μL which increased to 772 cells/μL when autoimmune diabetes was diagnosed. Our unique case involved an African American, whereas the previously reported patients were Japanese (4,7). Lastly, the etiology of IDDM or DKA (6,9-14) was unclear given negative GAD, inconsistently reported C peptide, and the ability to discontinue insulin in 3 cases (10,12,14). The CD4 count range for these 3 cases was 26 to 337 cells/μL at IDDM or DKA diagnosis. Given the implications of management of autoimmune and insulin-dependent diabetes, these cases demonstrate the importance of consideration of these diagnoses.

Adult-onset autoimmune diabetes is subclassified as either adult-onset type 1 diabetes mellitus (T1DM), latent autoimmune diabetes in the adult (LADA), or antibody-positive T2DM in an obese patient (15). LADA is diagnosed in antibody-positive patients ≥30 years of age who require insulin more than 6 months after diagnosis, a distinguishing feature from adult-onset T1DM (15). Our patient met the criteria for LADA. Progression to beta cell dysfunction is variable amongst patients with LADA. However, higher GAD antibody titer and greater number of autoantibodies are more predictive of beta cell dysfunction (15).

Metabolic syndrome occurs less often with LADA than T2DM, another distinguishing feature (15). Our patient had hypercholesterolemia with a lean body mass. C peptide, a marker of beta cell function, can also be useful in identifying autoimmune diabetes. However, C peptide requires careful interpretation. In one study, 78% of adult-onset T1DM cases had detectable C peptide 3 to 5 years after diagnosis and 16% had detectable C peptide >40 years after diagnosis, indicating residual beta cell function is possible even in T1DM (16). The presence of detectable C peptide in our patient does not exclude the possibility of autoimmune diabetes, and importantly his C peptide declined over time consistent with loss of beta cell function (Fig. 1).

Immune reconstitution may explain the development of autoimmune diabetes in this case. Immune reconstitution inflammatory syndrome (IRIS) occurs in approximately 16.1% (ranging from 11.1 to 22.9%) of individuals with HIV on ART (17). After CD4 count recovery, IRIS can present as a new or worsening infectious or non-infectious (e.g., autoimmune) disease (18). The mechanism of IRIS is unknown, but risk factors are disseminated opportunistic infection and CD4 count <50 cells/μL at the time of ART initiation (17,18). Specifically, Graves disease is one autoimmune disease reported in more than 40 patients after ART (19). Graves disease developed nearly 21 months after ART initiation in patients with a pretreatment median CD4 counts of 10 cells/μL (19). The proposed mechanism of Graves disease in this setting is loss of peripheral T

Table 2
Reported Cases of Confirmed Autoimmune Diabetes

Reference number	Age; sex; ethnicity	BMI (kg/m^2)	FH of DM	GAD (IU/mL); C peptide (ng/mL)	HIV history		At autoimmune DM diagnosis		Comorbidities
					HIV (years)	Nadir CD4 (cells/μL); concurrent VL (copies/mL)	CD4 (cells/μL); VL (copies/mL)	ART; duration of use	
5	48; M; NR	NR	NR	80.9; 0.2	6	NR; NR	500; UD	NR; NR	Hodgkin lymphoma (on nivolumab for 8 months)
7	40; M; JA	<30	-	34.8; 0.6	NR	<400; >1,200	>1,000; UD	lamivudine abacavir raltegravir; 29 months	NR
4 (case 1)	30; M; JA	24.2	+	606.0; 1.0	11	12; NR	>100; UD	lamivudine tenofovir lopinavir ritonavir; 18 months	hepatitis C thyrotoxicosis
4 (case 2)	31; M; JA	20.0	-	26,000.0; 0.7	17	14; NR	>100; UD	lamivudine sanilvudine lopinavir ritonavir; 10 months	hepatitis C
4 (case 3)	68; F; JA	19.1	-	1,023.0; 0.4	5	19; >10,000	~200; UD	lamivudine etravirine ritonavir darunavir raltegravir; 55 months	Graves disease
8	8; F; LAT	NR	-	4.4; 1.3	8	"normal"; UD	"normal"; UD	stavudine lamivudine abacavir; 6 years	anti-parietal cell antibody (+)

Abbreviations: + = positive; - = negative; AA = African American; ART = anti-retroviral; BMI = body mass index; CKD = chronic kidney disease; CMV = cytomegalovirus; DM = diabetes mellitus; FH = family history; GAD = glutamic acid decarboxylase; HTN = hypertension; JA = Japanese; LAT = Latino; M = male; NR = not reported; UD = undetectable; VL = viral load.

cell tolerance, ultimately impacting tolerance to thyroid tissue (19). Further studies are necessary to confirm the true mechanism.

Similarly, autoimmune diabetes has been reported in individuals with HIV on ART. One case series described 3 patients diagnosed with autoimmune diabetes after ART initiation, initially requiring oral medications or no anti-hyperglycemic medications (4). After consistent ART use, their CD4 counts improved and glycemic control worsened 9 to 55 months later, requiring insulin initiation. On retrospective laboratory analysis, GAD antibody was initially negative but became detectable after CD4 count recovery. Elevated GAD antibodies supported the diagnosis of autoimmune diabetes; the temporal relationship between GAD antibody development and CD4 count recovery suggested immune reconstitution might play a role (4).

The mechanism of beta cell dysfunction in HIV has been evaluated. One study investigated individuals with HIV not taking stavudine or didanosine and without a diagnosis of diabetes (to avoid the confounding factors of glucose toxicity, lipodystrophy, and insulin resistance) (20). Four groups of individuals were evaluated: (*1*) HIV positive with CD4 ≥350 cells/μL off ART for 6 months, (*2*) HIV positive with CD4 <350 cells/μL off ART for 6 months, (*3*) HIV positive with suppressed viral load on ART, and (*4*) HIV negative. Beta cell function measured by HOMA%B was no different in HIV negative than HIV positive individual off ART, suggesting HIV itself may not be associated with beta cell dysfunction. However, beta cell function measured by HOMA%B was lower in HIV positive individuals with CD4 <350 cells/μL than HIV-individuals, potentially suggesting an association

between ART and beta cell dysfunction. Further investigation is necessary to determine the exact mechanism of beta cell dysfunction in this population. Future studies may consider a longitudinal evaluation of patients with inclusion of CD4 count changes, the presence or absence of autoantibodies, and should use the presence of diabetes as a clinical outcome.

CONCLUSION

Our case report describes a patient diagnosed with diabetes after ART initiation for HIV. Although initially misclassified as T2DM, the presence of GAD antibody later confirmed autoimmune diabetes. Based on the severity of immune deficiency before ART, immune reconsti-

Table 3
Reported Cases of Diabetic Ketoacidosis and Insulin-Dependent Diabetes of Unclear Etiology

Reference number	Age; sex; ethnicity	BMI (kg/m^2)	FH of DM	GAD (IU/mL); C peptide (ng/mL)	HIV history		At diagnosis		Comorbidities
					HIV (years)	Nadir CD4 (cells/μL); concurrent VL (copies/mL)	CD4 (cells/μL); VL (copies/mL)	ART; duration of use	
6	40; M; JA	NR	NR	<5; 0.03	new diagnosis	28; NR	28; NR	none	CMV and PCP pneumonia, adrenal insufficiency, *Klebsiella pneumonia* and *Staphylococcus aureus* bacteremia
10	30; F; AA	21.0	-	negative; 1.9 about 4 months after diagnosis	3 years	26; 881,000	26; 881,000	zidovudine lamivudine abacavir; 3 years	IDDM/DKA (though eugylcemic 4 months later without insulin requirement), cerebral toxoplasmosis, HIV-related neuropathy, *Mycobacterium avium* infection, CMV gastritis, CMV retinitis
11	49; M; CA	NR	-	NR; NR	2 years	0; 400,000	80; <50	indinavir lamivudine stavudine; 2 years	new DM/DKA (presumed T2DM from protease inhibitor)
12	54; M; NR	NR	-	NR; "normal"	3 years	337; NR	337; NR	zidovudine; 5 months	cutaneous Kaposi sarcoma (treated with IFN 10 days prior), insulin later discontinued
13	37; M; CA	NR	+	NR; NR	NR	72; NR	180; NR	zidovudine; 3 months	IDDM/DKA, PCP pneumonia
14	24; M; CA	NR	-	NR; 0.6	5 years	<200; NR	<200; NR	zidovudine; 2 years	C peptide later normalized and insulin discontinued
9	29; M; NR	NR	NR	NR; 0.9	6 months	NR; NR	CD4 20%; NR	NR; NR	NR

Abbreviations: + = positive; AA = African American; ART = anti-retroviral; BMI = body mass index; CA = Caucasian; CKD = chronic kidney disease; CMV = cytomegalovirus; DKA = diabetic ketoacidosis; DM = diabetes mellitus; FH = family history; GAD = glutamic acid decarboxylase; HTN = hypertension; IDDM = insulin-dependent diabetes mellitus; IFN = interferon; JA = Japanese; M = male; NR = not reported; PCP = pneumocystis pneumonia; T2DM = type 2 diabetes mellitus; VL = viral load.

tution was considered as the potential mechanism. This case highlights the importance of recognizing autoimmune diabetes, considering autoimmune diseases as a manifestation of IRIS, and the need for further evaluation into the relationship between autoimmunity and IRIS. Given the higher prevalence of diabetes amongst patients with HIV, it is important to consider an autoimmune etiology in those with difficult to control diabetes.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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