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CASE REPORT

An HIV-Infected Patient Developed Immune Reconstitution Inflammatory Syndrome Immune Reconstitution Inflammatory Syndrome After Antiretroviral Therapy and Was Diagnosed with Primary Immune Thrombocytopenia, Latent Autoimmune Diabetes in Adults, and Hashimoto Thyroiditis: A Case Report and Review of the Literature

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Introduction: Immune reconstitution inflammatory syndrome (IRIS) is closely associated with antiretroviral therapy (ART) and poses a clinical challenge in HIV management.

Case Presentation: This report describes an HIV-infected individual who developed Primary immune thrombocytopenia, latent autoimmune diabetes in adults, and Hashimoto thyroiditis after starting ART.

Conclusion: Antiretroviral therapy (ART) may result in thrombocytopenia, fluctuations in blood glucose levels, thyroid dysfunction, diabetic ketoacidosis (DKA), or thyroid crisis. Healthcare professionals should evaluate the potential links between immune reconstitution inflammatory syndrome (IRIS) and latent autoimmune diabetes in adults (LADA), immune thrombocytopenia (ITP), as well as Hashimoto thyroiditis (HT).

Keywords: HIV, IRIS, LADA, case report

Introduction

HIV weakens the immune system by reducing CD4+ T cells, increasing susceptibility to opportunistic infections.[1] Highly Active Antiretroviral Therapy (HAART) restores CD4+ T cell counts and strengthens immune responses, improving the quality of life for infected individuals. While HAART has reduced Acquired immunodeficiency syndrome (AIDS)-related deaths, it can trigger immune reconstitution inflammatory syndrome (IRIS), a poorly understood complication marked by excessive inflammation due to opportunistic infections, often seen early in treatment.[2] It is important to note that immune reconstitution syndrome, which occurs when HIV-positive patients begin HAART, can sometimes lead to an overactive immune response, which can even trigger or worsen thyroid diseases, causing various autoimmune diseases.[3] There have been reports of autoimmune diabetes in people living with HIV who are on antiretroviral therapy (ART), but such cases are relatively rare. Although the specific mechanism linking diabetes and HIV infection remains unclear, existing research suggests that immune reconstitution may play a role in this.

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Case Presentation

October 17th, 2024, a 54-year-old male was admitted to the hospital with a diagnosis of HIV antibody positivity for two months, jaundice (yellow eyes) for one month, and a generalized rash for one week. Two months prior, the patient tested positive for HIV antibodies and commenced antiretroviral therapy consisting of tenofovir, lamivudine, and efavirenz. One month after the regular follow-up, his liver function tests were normal. Subsequently, he developed progressive symptoms, including scleral icterus, skin jaundice, dark urine, and significant fatigue. A diffuse rash appeared on the chest and back one week before admission and gradually spread to involve the entire body. The patient also experienced nausea, vomiting, and anorexia. Laboratory investigations revealed a total bilirubin of 145.4 μmol/L, a direct bilirubin of 143.2 μmol/L, a CD4 T-cell count of 55/μL, and undetectable HIV RNA (<100 IU/mL).

Upon admission, tenofovir, lamivudine, and efavirenz were discontinued, and the patient received supportive treatments, including jaundice relief, hepatoprotection, transaminase reduction, anti-diarrheal therapy, antimicrobial prophylaxis, and red blood cell transfusion. Methylprednisolone was administered for allergic reactions. After one month, the patient's rash and liver function improved, and highly active antiretroviral therapy (HAART) was restarted using Bictegravir Sodium, Emtricitabine and Tenofovir Alafenamide Fumarate (B/F/TAF). Three days later, the platelet count decreased from 191 × 10^9/L to 92 × 10^9/L, and one week later, it further dropped to 15 × 10^9/L. A bone marrow biopsy was performed, revealing: (1) increased megakaryocyte quantity but impaired function; (2) low intracellular iron content; (3) disordered maturation of the granulocytic series. Bone marrow biopsy findings showed vigorous proliferation of hematopoietic cells, predominantly involving intermediate and late-stage granulocytes. Immunohistochemistry results included CD117 (+ in individual cells), CD34 (+ in separate cells), CD45 (+ in a few cells), Ki-67 (+ partially), myeloperoxidase (MPO) (+ mostly), negative for iron-containing cells, acid-fast bacilli, and reticulin staining (small amount of reticular fibers). Based on these findings, the patient was diagnosed with Primary immune thrombocytopenia (ITP).

The patient was treated with methylprednisolone. Nine days later, the platelet count recovered to 114 × 10^9/L, and methylprednisolone was tapered regularly post-discharge. Half a month later, the platelet count normalized, and the CD4 T-cell count increased to 247/μL.

Two months after discharge, the patient presented with new-onset symptoms, including fatigue, poor appetite, nausea, vomiting, xerostomia, and polyuria lasting one week. He had lost approximately 5 kg in weight, and his random blood glucose level upon admission was 24.8 mmol/L. Arterial blood gas analysis revealed a pH of 7.15, urine ketones (3+), and hydroxybutyric acid of 6.41 mmol/L. The patient was diagnosed with diabetic ketoacidosis (DKA). Following aggressive treatment, his condition improved. Laboratory tests confirmed glutamic acid decarboxylase antibody at 1158.70 IU/mL, tyrosine phosphatase antibody at 4.11 IU/mL, insulin autoantibody at 0.28 COI, islet cell antibody at 23.46 COI, HbA1c at 10.6% (free triiodothyronine at 5.22pmol/L, free thyroxine at 13.91pmol/L; thyroid-stimulating hormone at 0.01 μIU/mL, TPO-Ab at 18.50 IU/mL, TG-Ab at 6.42 IU/mL, TR-Ab 0.88 IU/L) (Table 1). Based on these findings, the patient was diagnosed with Latent Autoimmune Diabetes in Adults (LADA) and Hashimoto thyroiditis

Table 1 Characteristics and Laboratory Findings at the Diagnosis of Autoimmune Diabetes

Data Related to Diabetes	
Casual plasma glucose (mmol/L)	25.39
HbA1c(%)	10.6
Fasting serum insulin (μU/mL)	3.90
Fasting serum C-peptide (ng/mL)	0.46
Urine ketone body	3+
GAD-Ab(IU/mL)	1158.70
ICA(COI)	23.46
IAA(COI)	0.24
IA2-Ab(IU/mL)	3.45

(*Continued*)

Table 1 (Continued).

Thyroid Function Tests	
FT3(pmol/L)	5.22
FT4(pmol/L)	13.91
TT3(nmol/L)	1.48
TT4(nmol/L)	162.25
TSH(μIU/mL)	<0.01
TPO-Ab(IU/mL)	18.5
Tg-Ab(IU/mL)	6.42
TR-Ab(IU/L)	0.88
Data related to COR and ACTH	
8amCOR (nmol/L)	500.42
4pmCOR (nmol/L)	380.14
0amCOR (nmol/L)	358.66
8amACTH (ng/L)	62.54
4pmACTH (ng/L)	34.21
0amACTH (ng/L)	29.77

Notes: Normal ranges include the following: GAD-Ab, less than 10.0 IU/mL; ICA, less than 1.1 COI; IAA, less than 1.1 COI; IA2-Ab, less than 10.0 IU/mL; FT3 (3.67–6.0pmol/L); FT4 (7.86–21.1pmol/L); TT3 (1.01–2.48nmol/L); TT4 (-69.97–152.5nmol/L); TSH (0.56–5.91μIU/mL); TPO-Ab, less than 5.61IU/mL; Tg-Ab, less than 4.11IU/mL; TR-Ab, less than 1.90 IU/L.

Abbreviations: GAD-Ab, glutamic acid decarboxylase antibody; ICA, islet cell cytoplasmic antibodies; IAA, insulin autoantibodies; IA2-Ab, tyrosine phosphatase-related IA-2 antibodies; FT3, free triiodothyronine; FT4, free thyroxine; TT3, triiodothyronine; TT4, thyroxine; TSH, thyroid-stimulating hormone; TPO-Ab, antithyroid peroxidase antibody; Tg-Ab, antithyroglobulin antibody; TR-Ab, thyrotropin receptor antibody; COR, cortisol; ACTH, adrenocorticotropic hormone.

(HT). Currently, the regimen of MDI is insulin glargine as basal insulin and insulin aspart as prandial insulin, with ongoing endocrinological follow-up and thyroid function follow-up (Figure 1).

Discussion

The human immunodeficiency virus (HIV) compromises the immune system by reducing the number of CD4+ T lymphocytes, making patients more vulnerable to opportunistic infections. Highly active antiretroviral therapy (HAART) is instrumental in restoring CD4+ T lymphocyte counts and enhancing the immune response against pathogens. This improvement in immune function has dramatically improved the quality of life and health outcomes for

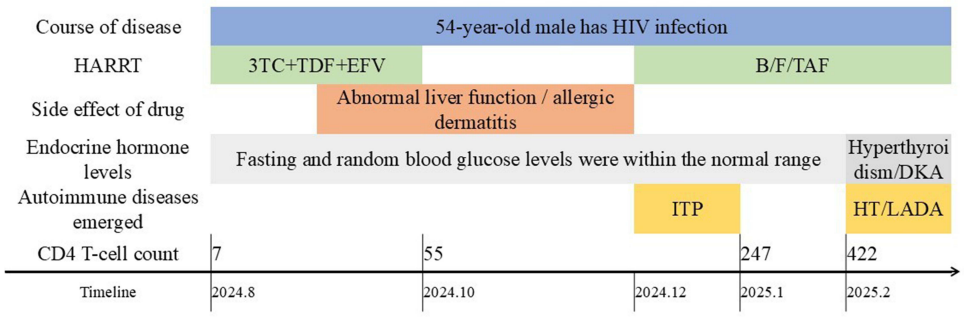

Figure 1 Progression Course of the Current Case.

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Table 2 LADA Cases Have Been Reported in HIV Patients on ART

report	Case	Age (years)	Sex	BMI (kg/m^2)	Family History of Diabetes	CD4 Count at nadir (Cells/l)	CD4 Count (Cells/l)	GAD-Ab (U/mL)	HIV Infection Duration at Diabetes Diagnosis	HAART
Takarabe 2010[16]	1	30	M	24.2	—	12	>100	606	11Y	Lamivudine tenofovir lopinavir ritonavir
Takarabe 2010[16]	2	31	M	20	—	14	>100	26,000	17Y	Lamivudine sanilvudine lopinavir ritonavir
Takarabe 2010[16]	3	68	F	19.1	—	19	200	1023	5Y	Lamivudine etravirine ritonavir darunavir raltegravir
Kamei S 2015[18]	4	40	M	NR	—	250	>1000	34.8	16m	Lamivudine abacavir raltegravir
Kyrstin L 2020[17]	5	68	M	22.4	+	2	772	>250	30Y	Lamivudine abacavir dolutegravir; intermittently
Min-ChunYeh 2023[3]	6	36	M	25.2	NR	15	429	>2000	2Y	Bictegravir sodium,emtricitabine and fenofovir alafenamide fumarate
Taguchi 2023[19]	7	40	M	17.6	—	52	291	>2000	9Y	NR
Our case 2025	8	54	M	17.3	—	13	422	1158.70	6m	Bictegravir sodium,emtricitabine and fenofovir alafenamide fumarate

Abbreviations: Y, years; M, month; M, male; F, female; NR, not report;-, negative; +, positive.

individuals living with HIV. Despite the significant progress HAART brought in reducing HIV-related deaths, challenges persist regarding its use. Since its introduction, various side effects of HAART and its potential interactions with other medications have been reported. These side effects can range from mild allergic reactions to severe idiosyncratic responses, hematological abnormalities, and changes in drug metabolism.[4] One notable complication associated with HAART is the immune reconstitution inflammatory syndrome (IRIS). IRIS is a condition that remains incompletely understood, with its precise mechanism still unclear.[5] It involves an exaggerated and dysregulated inflammatory reaction to opportunistic infections, typically occurring within the first six months of HIV/AIDS treatment.

First recognized in the 1990s, IRIS represents a potential challenge linked to HAART. It may reduce treatment adherence, foster drug resistance, accelerate the progression of HIV to AIDS, and negatively impact the quality of life for affected individuals.[6,7] IRIS is associated with substantial morbidity and mortality rates among HIV-positive patients.[8]

The characteristic of HIV infection is the progressive damage to the immune system, which leads to a series of opportunistic infections as well as immunological and hematological complications. The association between ITP and AIDS was first discovered in 1982.[9] With the application of HAART, the incidence of HIV-related thrombocytopenia has significantly decreased.[10]

Latent Autoimmune Diabetes in Adults (LADA) is an autoimmune disorder that shares certain genetic, immunological, and clinical characteristics with both Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). It is also referred to as type 1.5 diabetes or slow-onset diabetes in adults. In 2019, the World Health Organization (WHO) regarded LADA as mixed diabetes between T1DM and T2DM,[11] and in 2020, the international panel also considered LADA to be diabetes between T1DM and T2DM.[12] In 2021, Chinese experts held that LADA should be classified as a subtype of slowly progressing autoimmune T1DM based on etiology, and in 2022, the American Diabetes Association (ADA) proposed that LADA should be categorized as a type of T1DM.[13]

Treating LADA is challenging due to its unique characteristics and limited treatment options. An individualized plan based on clinical and biochemical factors is essential to control blood glucose, protect β-cell function, and minimize complications. Exogenous insulin cannot fully replace endogenous insulin. Early insulin therapy can slow β-cell decline, support remaining β-cell function, and reduce insulitis severity.[14] Timely intervention improves the long-term quality of life for LADA patients. Adequate blood glucose management is critical to prevent complications.[15]

In our review of the literature,8 LADA cases have been reported in HIV patients on ART, which are potentially related to IRIS (Table 2). Takarabe et al[16] reported three Japanese patients who developed autoimmune diabetes after starting ART. Before ART, their GAD-Ab tests were negative, and CD4+ counts were below 20 cells/μL. GAD-Ab turned positive 6–38 months later, as CD4+ counts increased significantly. Lane et al[17] reported an African American HIV-infected individual diagnosed with T2DM within 10 years of starting ART. NIAD was initially used, followed by insulin therapy 13 years later. 18 years after the T2DM diagnosis, despite good insulin adherence and a monitored lifestyle, the patient was referred to a diabetes clinic for poor glycemic control. GAD-Ab testing was positive, with CD4 count rising from 2 cells/μL to 772 cells/μL at autoimmune diabetes diagnosis. Min C et al[3] reported a 36-year-old man with HIV had a CD4 count of 15.53/μL before ART, which increased to 429.09/μL after 9 months. At 11 months of ART, he was hospitalized for DK and Graves' disease (GD). Following DKA resolution, tests revealed impaired pancreatic β-cell function and elevated anti-GAD and anti-IA2 titers.

Abnormal thyroid function tests are commonly observed in patients with HIV infection. The well-recognized association between Graves' disease and IRIS typically occurs following the initiation of ART.[20] Hashimoto thyroiditis were described in HIV-infected people as a manifestation of delayed IRIS.[21]

It is important to highlight that antiretroviral therapy (ART) can lead to fluctuations in blood glucose levels, thyroid dysfunction, and in severe cases, DKA or thyroid storm. Healthcare providers should be aware of the connection between ART-induced IRIS and LADA. Recognizing this relationship can aid in minimizing subsequent complications and preventing more serious endocrine disorders from developing.

Conclusion

This case underscores the critical importance of recognizing autoimmune diabetes and proposes that autoimmune diseases may represent one manifestation of IRIS. Further investigation into the relationship between these two

conditions is warranted. Considering the elevated prevalence of diabetes among individuals with AIDS, it is essential to evaluate autoimmune factors in patients presenting with refractory diabetes. This report only discusses the possible correlation between IRIS and LADA based on the existing cases and a few reported cases. However, a large amount of basic and clinical data is still needed to support and verify the underlying mechanism of this correlation.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation. For data inquiries, please contact yll8324@163.com.

Ethics Approval and Consent to Participate

All procedures carried out in the study involving human participants conformed to the ethical standards of the Ethics Committee of Hangzhou Xixi Hospital. The ethics committee approved the waiver in this case report based on the moral standards for publishing the case details.

Consent for Publication

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; have drafted, revised, or critically reviewed the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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