



Graves' Disease As a Manifestation of IRIS in an HIV Patient: Case Report

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Abstract

Highly Active Anti-Retroviral Therapy (HAART) may be related to Immune Restoration Inflammatory Syndrome (IRIS). Although rare, Graves' disease may present as part of IRIS but usually presents 12-24 months after HAART initiation. We report a case of hyperthyroidism that developed 34 months after initiation of a new HAART regimen.

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Introduction

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) have become major health care problems worldwide over the last several decades. Highly Active Anti-Retroviral Therapy (HAART) leads to a reduction in morbidity and mortality and improves the prognosis of an HIV-infected patient [1]. However, after treatment initiation, some patients develop paradoxical clinical deterioration caused by restoration of their immune system against both infectious and noninfectious antigens [2,3]. This has been characterized as Immune Restoration Disease (IRD), immune reconstitution syndrome/Immune Recovery Syndrome (IRS), or Immune Restoration Inflammatory Syndrome (IRIS) [2].

Most IRIS events occur during the first six months of HAART initiation [4] and opportunistic infections probably because of the imbalance in reconstitution of effect or and regulatory T-cells. Although extremely uncommon, autoimmune diseases may take part in or follow IRIS.

Graves' disease (GD), an autoimmune condition that leads to the production of anti-Thyroid Stimulating Hormone (TSH) receptor antibodies, is the leading cause of hyperthyroidism both in the general population and HIV-infected individuals. When present, Graves' disease seems to be part of IRIS since it is usually diagnosed 12-24 months after HAART initiation, but some cases occur five years after new therapy initiation. The difference in timing may be explained by the distinction in types of



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cluster of differentiation (CD4) cells that cause an increase in a biphasic pattern after HAART initiation; the first phase represents the release of predominantly memory CD4 cells from lymphoid tissue followed by the second phase, which occurs month later, and is represented by expansion of naive CD4 cells with accompanying changes in T-helper cytokine production profiles [5].

We report a case of hyperthyroidism caused by GD that developed after HAART initiation.

Case report

A 24-year-old Brazilian male HIV-positive patient was treated with antiretroviral medication and showed good therapeutic response. He was referred from the infectious diseases outpatient clinic to the emergency department of our university hospital with a goiter and symptoms (palpitation, high blood pressure, fine tremor, weight lost, diaphoresis, and ocular proptosis) that started three months earlier. Upon physical examination, his blood pressure was 150/60 mmHg with a heart rate of 154 bpm and sinus rhythm on the electrocardiogram. The thyroid was approximately 100 g and homogeneously enlarged.

The patient was diagnosed with HIV at seven years old (indeterminate transmission). He had a low lifetime compliance to treatment. Thirty-four months prior to presentation, he started a new regimen of Tenofovir, Lamivudine, Darunavir/Ritonavir, and Dolutegravir and had a good response. His HIV RNA lev-

els were undetectable for 19 months. His CD4 T-cell count had recovered two months before he presented with hyperthyroidism. CD4 T-cell count and HIV RNA levels are shown in Table 1. He had no personal or family history of autoimmune or thyroid diseases.

Laboratory tests showed TSH and free T4 levels of <0.004 (normal range 0.40–4.0 ng/dL) and 5.7 (0.89–1.76mcg/dL) respectively, confirming the hyperthyroidism diagnosis. He also presented with a mild anemia (hemoglobin levels of 11.0) and mild alterations in alkaline phosphatase and gamma-glutamyl-transpeptidase (470 U/L and 94 U/L, respectively). His records showed normal TSH and free T4 levels before he started the new HAART regimen (Table 1).

The patient was diagnosed with probable IRIS-related thyrotoxicosis and started on methimazole (20 mg) and propranolol (120 mg/day) with reevaluation in five days. He returned to the endocrinology outpatient clinic still presenting some signs and symptoms of thyrotoxicosis (goiter, proptosis, tachycardia [104 bpm], and fine tremors). Laboratory tests indicated that he was still had suppressed TSH levels (0.010 ng/dL) and high free T4 levels (> 6.00 mcgUI/mL). On this occasion, he presented with laboratory dosage of autoantibodies. TSH receptor autoantibody and thyroperoxidase antibody (TRAB and anti-TPO) levels were 14.5 UI/L (<1.75 UI/L) and 213.0 UI/mL (<35 UI/mL), respectively. The methimazole dose was adjusted to 30 mg/day. He returned a month later with symptom remission.

Figure 1: CD4 T-cell count and HIV RNA levels since the start of the new HAART regimen until the onset of symptoms and evolution of TSH and free T4 levels before and after the onset of symptoms.

	RNA VIRAL COPIES	CD4+ T CELLS COUNT	TSH	FREE T4
01-08-2013	58,772	215 cells/mcgL	----	----
03-12-2015	12,658	75 cells/mcgL	1,77 ng/dL	1.25 mcgUI/mL
21-01-2018	79	523 cells/mcgL	----	----
08-03-2018	----	----	0.004 ng/dL	5.70 mcgUI/mL
02-04-2018	----	----	0.010 ng/dL	> 6.00 mcgUI/mL

Reference values of TSH (0.40-4.0ng/dL) and Free T4 (0.89-1.76 mcgUI/mL)

Discussion

Initially, an autoimmune disease affecting patients with an immune deficiency syndrome sounds paradoxical. As described in our case report, although GD is rare, it may be part of the IRIS syndrome. HIV infection causes a persistent decline in CD4+ naive and memory cells, an increase in the peripheral blood inactivated T cells, and thymic dysfunction [6]. HIV prognoses changed after initiation of HAART since HIV patients undergoing a HAART regimen present with a restoration in CD4 lymphocyte count. This immune recovery occurs in a biphasic manner [7]: (1) an initial phase of CD4+ cell recovery lasting six months after treatment initiation therapy and includes an increase in CD4+ memory cells and (2) a second phase starting six months after treatment that is marked by an increase in CD4+ naive cells and changes in T-helper cytokine production [5]. Reconstitution of naive cells in the second phase, especially the production of regulatory T cells, may be impaired as a result of the HIV-induced thymic dysfunction [8]. This impairment leads to dysregulation in the immune system that culminates in an interruption in tolerance related to both aberrant B and T cells. This dysregulation is the context in which autoimmune diseases present with GD as a late complication after HAART initiation. Predisposing factors to the development of IRIS autoimmune

diseases are the extent and duration of immune deficiency, velocity of immune reconstitution, and high-fold increase in CD4 T lymphocytes in addition to genetic susceptibility (polymorphisms in the cytokine genes, interleukin [IL]-6 and -12, and Tumor Necrosis Factor [TNF]) [7]. Gilquin et al. first described Graves' IRIS in 1998 [9], and following that report, a few other cases have been reported in the literature [3,8-14]. Recently, a large single center cohort study involving 2437 patients demonstrated a hyperthyroidism prevalence of 1.01% in HIV patients over a course of 11 years [14]. There were no differences between men and women. The age at diagnosis varied from 24 to 55 years old (mean of 39 years), and the onset of reconstitution Grave's disease occurs 12–58 months (mean 19 months) after HAART initiation. There was a significantly lower CD4+ T cell count at baseline in the group who presented with hyperthyroidism. An immune recovery of 75% higher in this group after HAART initiation was noted. There was an association between hyperthyroidism and non-nucleoside reverse transcriptase inhibitors, particularly Efavirenz. Most diagnoses were confirmed by the presence of TSHR and TPO antibodies. None of the patients had family histories of thyroid disease. Other auto antibodies were not detectable in the patients [3, 8-14]. These cases had the common finding that at baseline, patients presented with profound immune deficiency followed by rapid

and large increases in the CD4 T-cell count as a result of HAART; these two factors appear to be related to the development of immune restoration disease. The treatment for GD associated with immune restoration syndrome does not differ from the standard treatment for hyperthyroidism. Patients may be treated with Anti-Thyroid Drugs (ATD), such as methimazole or propylthiouracil, or with definite therapies, such as iodine radiation or surgery. The choice should be individualized and based on patient's risks and preferences. Since a typical HIV-infected patient undergoing HAART is more prone to hepatotoxicity (notably patients with B or C virus forms), early definitive treatment may be a good choice for that patient. Currently, there are insufficient data in favor of thyroid function screening tests for asymptomatic HIV patients [15], and the diagnosis should be based on clinical symptoms and laboratory tests.

Our patient case agrees with most of the previously reported cases although there was a longer period since he was started on HAART (34 months before the onset of hyperthyroidism symptoms), and he also presented a baseline immune deficiency showing a great response with drastically reduced viral loads at the time of Graves' IRIS diagnosis. Also in agreement with reports in the literature, he had no personal or family history of autoimmune or thyroid diseases. His clinical and laboratory diagnoses were performed in the same manner as any other GD patients with typical symptoms and presence of TSHR. Since there was no history of B or C viral hepatitis, we opted for ATD therapy with methimazole, yielding a good clinical response.

Conclusion

Physicians, especially infectious disease specialists who manage HIV patients, must be aware of the possibility of thyroid dysfunction as part of IRIS, especially during the 60-month period after HAART initiation. There is no protocol for thyroid function testing, but a TSH test with T4 on an annual basis may be plausible. Patients with long-term HIV treatment noncompliance may be more prone to this association.

We suggest that hyperthyroid management should be the same as for a non-HIV patient, remembering the need for liver monitoring if ATD is selected as the treatment choice.

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Disclosure

No potential conflict of interest relevant to this article was reported.

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