REPEATED PRESENTATION OF GRAVES' DISEASE AS A MANIFESTATION OF IMMUNE RECONSTITUTION SYNDROME IN AN HIV-INFECTED PATIENT TAKING HAART: CASE REPORT

Klaudija Višković[1], Lorna Stemberger[2], Zoran Brnić[3] and Josip Begovac[4]

[1]Department of Radiology and Ultrasound, University Hospital for Infectious Diseases, [2]resident, University Hospital for Infectious Diseases; [3]Merkur University Hospital and University of Zagreb, School of Medicine, [4]Center for HIV/AIDS Infection, University Hospital for Infectious Diseases and University of Zagreb, School of Medicine, Zagreb, Croatia

SUMMARY – An HIV-infected patient who experienced immune reconstitution after highly active antiretroviral therapy (HAART) (increase in CD4 T-cell count from 84/mm^3 to 310/mm^3) presented with severe Graves' disease twice, after commencing and recommencing HAART. At the first episode of Graves' disease, 21 months after the introduction of HAART, the symptoms of thyroid dysfunction vanished without any specific treatment, but were associated with termination of taking HAART. At the second episode, 5 years after recommencing HAART, the patient continued taking HAART and commenced antithyroid therapy with thiamazole. Graves' disease developed after a long period, while the patient was in good condition and when complications resulting from HAART were not expected. No features of any autoimmune disease were diagnosed before HAART initiation.

Key words: *HIV infection; Antiretroviral therapy; Graves' disease*

Introduction

The immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients initiating Highly Active Antiretroviral Therapy (HAART) results from restored immunity to specific infectious or non-infectious antigens[1]. The inflammatory response can result in autoimmune disorders such as Graves' disease[2,3].

Graves' disease is characterized by the presence of serum thyrotropin-receptor (TSHR) autoantibodies that stimulate the TSH receptor of thyrocytes[4-6]. The immunoregulatory abnormalities underlying the production of TSHR autoantibodies are incompletely understood in HIV-infected patients who develop Graves' disease during the course of HAART-induced IRIS[7].

We report a case of an HIV-infected patient who presented with severe Graves' disease twice, after commencing and recommencing HAART.

Correspondence to: *Klaudija Višković, MD, PhD,* Department of Radiology and Ultrasound, University Hospital for Infectious Diseases, Mirogojska 8, HR-10000 Zagreb, Croatia
E-mail: viskovick@gmail.com

Received February 1, 2012, accepted April 20, 2012

Case Report

A 48-year-old Caucasian woman was found to be HIV-1 antibody positive in February 1999, acquired through heterosexual contact. At the same time, at the HIV/AIDS Outpatient Clinic of the University Hospital for Infectious Diseases (UHID) in Zagreb she had CD4 T-cell count of 84/mm^3 and the HIV

plasma viral load was 8270 copies *per* mL. The patient rejected taking HAART until January 2001, when cryptosporidiosis developed. HAART was commenced consisting of stavudine, lamivudine and efavirenz. Normal TSH, tri-iodothyronine (T_3) and thyroxine (T_4) levels were documented by laboratory tests. There was no past personal or family history of thyroid disease. The therapy suppressed viral replication, and in September 2002, she had undetectable viral RNA and a high blood CD4 T-cell count (310/mm^3). At that time, she presented with heart palpitations, hand tremor and a 5 kg weight loss over a 2-month period. These symptoms were associated with suppressed TSH (0.03 mU/L) and elevated T_3 (8.5 nmol/L) and T_4 (292.6 nmol/L) concentrations. The patient decided to stop taking HAART and did not present for follow-up visits until February 2005. Meanwhile, the symptoms of thyroid dysfunction disappeared without any specific treatment, but were associated with termination of taking HAART.

At the follow-up visit in February 2005, the patient presented with fever, cough, diarrhea, seborrheic dermatitis and oropharyngeal candidiasis. Laboratory findings revealed extremely low CD4 T-cell count (1 cell/mm^3) and a high number of HIV-1 RNA copies (679 000/mL). HAART was introduced again, consisting of zidovudine, lamivudine and lopinavir. Seven months later, in September 2005, at the follow-up visit, she had no thyroid dysfunction symptoms and normal TSH, T_3 and T_4 levels, no viral RNA but still low T-cell count (27 cells/mm^3).

Five years after re-commencing HAART, in February 2010, typical signs and symptoms of hyperthyroidism developed again (hand shaking, exophthalmos, systolic heart murmur, tachycardia, and enlarged thyroid gland). The examination of thyroid function revealed extremely elevated T_4 (>309 nmol/L), free T_4 (FT_4) (58 pmol/L), T_3 (>9.24 nmol/L), free T_3 (FT_3) (29 pmol/L) and low TSH (<0.004 mU/L) levels. Elevated levels of antithyroid peroxidase (>600 IU/mL) and antithyroglobulin (904 IU/mL) autoantibodies were also recorded. Antithyroid therapy with thiamazole (3x20 mg) and beta-blocker therapy with atenolol (1x25-50 mg) was promptly commenced. At that time, due to constant HAART administration, serum HIV-1 RNA was undetectable and CD4 T-cell count was high (389/mm^3).

The thyroid function clinically normalized 4 weeks after the specific treatment had been initiated, as well as T_3 and T_4 levels, only TSH value remained low (<0.002 IU/L).

Discussion

Graves' disease is most commonly diagnosed 12-36 months after HAART initiation[8]. Chen *et al*. indicate that patients who develop autoimmune thyroid disease have a significantly lower mean baseline CD4 T-cell count and experience a significantly higher rise in the CD4 T-cell count (mean 355.1 cells/mL)[9].

In our patient, autoantibodies were absent before immune restoration, ruling out exacerbation of the preexisting autoimmune disease. Hyperthyroidism in our patient occurred twice, both times after commencing HAART, for the first time 21 months after initiating therapy and for the second time 5 years later. Both times the occurrence of Graves' disease was associated with an increasing number of CD 4 T-cells (310 and 389 CD4 T-cells/mm^3, respectively). These findings imply that the reactivation of hyperthyroidism was connected with successful HAART effect. After the first episode of Graves' disease, the patient decided to stop taking antiretroviral therapy. Consequently, thyroid symptoms disappeared without any specific treatment. We suggest that the aggravation of HIV-infection, a decreased number of CD4 T-cells and an elevated number of HIV-1 RNA in serum correlate with amelioration of thyroid dysfunction. Our data pointed to the CD4 T-cell number of 300/mm^3 as a significant factor for developing Graves' disease in HIV-1 positive patients taking HAART. During the follow-up period, our patient had CD4 T-cell number higher than 300/mm^3 at three time points, and in two of those times she developed Graves' disease.

Clinicians should be aware of the possibility of Graves' disease-IRIS in HIV-1 infected individuals in different periods after commencing HAART, following viral suppression and significant immune restoration.

References

1. MURDOCH DM, VENTER WD, van RIE A, FELDMAN C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. AIDS Res Ther 2007;4:9.
2. PRICE P, MATHIOT N, KRUEGER R, STONE S, KEANE M, FRENCH MA. Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. J Clin Virol 2001;22:279-87.
3. SHELBURNE SA 3rd, HAMILL RJ, RODRIGUEZ-BARRADAS MC, *et al*. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine 2002;81:213-27.
4. WEETMAN AP. Graves' disease by any other name? Thyroid 2000;10:1071-2.
5. WEETMAN AP. Graves' disease. N Engl J Med 2000;343:1236-48.
6. MARTINKO J, CIGROVSKI-BERKOVIĆ M, BEČEJAC B, SOLTER D, SOLTER M. Development of Graves' disease following radioiodine treatment for autonomously functioning thyroid adenoma: case report. Acta Clin Croat 2011;50:615-7.
7. FRENCH MA, LEWIN SR, DYKSTRA C, KRUEGER R, PRICE P, LEEDMAN PJ. Graves' disease during immune reconstitution after highly active antiretroviral therapy for HIV infection: evidence of thymic dysfunction. AIDS Res Hum Retrovirus 2004;20:157-62.
8. HOFFMANN CJ, BROWN TT. Thyroid function abnormalities in HIV-infected patients. Clin Infect Dis 2007;45:488-94.
9. CHEN F, DAY SL, METCALFE RA, SETHI G, KAMPEBWA MS, BROOK MG, *et al*. Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease. Medicine 2005;84:98-106.

Sažetak

PONOVLJENA PREZENTACIJA GRAVESOVE BOLESTI KAO MANIFESTACIJE SINDROMA IMUNE REKONSTITUCIJE U BOLESNICE ZARAŽENE HIV-om KOJA UZIMA ANTIRETROVIRUSNE LIJEKOVE

K. Višković, L. Stemberger, Z. Brnić i *J. Begovac*

Bolesnica zaražena HIV-om u koje se razvio sindrom imune rekonstitucije nakon antiretrovirusnog liječenja (ARL) (porast broja stanica CD4 s 84/mm^3 na 310/mm^3) prezentirala se u dva navrata s Gravesovom bolešću, na početku liječenja ARL-om i nakon stanke u liječenju. Tijekom prve epizode 21 mjesec nakon uvođenja ARL-a simptomi tiroidne disfunkcije nestali su bez specifičnog liječenja, ali su bili povezani s prestankom uzimanja ARL-a. Tijekom druge epizode 5 godina nakon ponovnog uzimanja ARL-a bolesnica je nastavila uzimati ARL i započela s antitiroidnim lijekom tiamazolom. Gravesova bolest se ponovno javila nakon dugog razdoblja kad je bolesnica bila u dobrom općem stanju i kad se komplikacije vezane uz ARL više nisu očekivale. Prije uzimanja ARL-a bolesnica nije pokazivala nikakve znakove autoimune bolesti.

Ključne riječi: *HIV-infekcija; Antiretrovirusni lijekovi; Gravesova bolest*