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Grave's Disease as A Manifestation of Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV Patients Who are Later Diagnosed with Cervical Cancer: A Case Report

Putu Ayu Sri Saraswati[1], Wira Gotera[1]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia

Corresponding Author: Putu Ayu Sri Saraswati

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ABSTRACT

Grave's Disease (GD) after giving Active Antiretroviral Therapy (ART) to HIV patients is one of the manifestations of Immune Reconstruction Inflammatory Syndrome (IRIS). Complaints and clinical symptoms of Grave's IRIS usually appear in 8-33 months since the use of ART.

A 40-year-old woman was diagnosed with HIV with comorbid pulmonary tuberculosis (TB) infection. The patient regularly took ART and had finished taking TB drugs for 6 months, and the pulmonary TB was declared cured. However, the patient began to complain and showed clinical symptoms of hyperthyroidism. After receiving anti-thyroid medication, the patient has no complaints related to thyroid disease. Six months later, the patient experienced frequent vaginal bleeding. After being evaluated by the Obstetrics and Gynecology section, the patient was diagnosed with cervical cancer.

Abnormality of thyroid function test in HIV patients was common, but only 1-2% of HIV patients showed signs of thyroid disorder. However, few cases still show GD as a manifestation of IRIS in HIV patients receiving ART. Dysregulation of the immune system in IRIS-HIV condition and long-standing inflammatory response of HIV (innate and adaptive immune cells involvement, MCH class I & MCH class II expression, TGFβ effect, immune-modulating drugs effect, and effect of reactive oxygen species) promote progression of cancer.

Keywords: Grave Disease, IRIS, Cancer, HIV

INTRODUCTION

The early use of antiretroviral therapy (ART) provides bright hope for the life expectancy of HIV patients.[1] ART in HIV patients will improve the immune system and reduce morbidity and mortality from opportunistic infections. However, some patients show different clinical responses to improving the immune system after receiving ART.[2] This phenomenon is known as Immune Reconstruction Inflammatory Syndrome (IRIS), in restoring the inflammatory response in both infectious and non-infectious processes.[3] Symptoms of IRIS in patients with HIV are most often found in the infectious process, in the form of reactivation of opportunistic infections after several weeks until months of receiving ART. Where reactivation of this opportunistic infection is accompanied by immunological improvement (increased CD4 cell count).[4]

IRIS in non-infectious processes can be a variety of autoimmune diseases.[5] Grave's Disease (GD) is an autoimmune condition that includes IRIS in HIV patients. There is a failure of immune reconstruction by T cells, especially nave CD4, so an

autoimmune process occurs in the thyroid gland.6 Prolonged inflammatory conditions can trigger cancer due to HIV infection and autoimmune conditions.[4]

CASE ILLUSTRATION

A 40-year-old woman, diagnosed with HIV for thirteen years, with risk factors due to drug use (intravenous drugs user/IVDU), tattoos, and sexual multi-partners. The patient was diagnosed with HIV initial CD4: 14 cells/µL and comorbid pulmonary tuberculosis (TB) infection. Initial treatment was antiretroviral therapy (zidovudine, lamivudine, efavirenz), cotrimoxazole, and TB drugs category I. At that time, the patient had no complaints and clinical symptoms of thyroid disorders (hyperthyroid or hypothyroid). The patient's family also did not have a thyroid function disorder.

The patient regularly took ART and had finished taking TB drugs for 6 months, and the pulmonary TB was declared cured. However, the patient began to complain and showed clinical symptoms of hyperthyroidism. The patient had a weight loss of 5 kg in 6 months, palpitations, finger tremors, difficulty in defecation, enlargement of the thyroid gland, and exophthalmos (Figure 1.). There were no complaints of disturbances in menstruation and genital organs. From the results of the thyroid function test, there was an increase in thyroid hormone, free thyroxine (fT4): 5.87 ng/dL, and suppression of Thyroid Stimulating Hormone (TSH): <0.003 IU/mL. Ultrasonographic examination of the thyroid gland revealed diffuse enlargement of both thyroid glands with hypervascularization according to Grave's Disease. The eye examination revealed exophthalmos Oculi Dextra and Sinistra (Grave's Ophthalmopathy/GO) and CD4: 375 cells/µL, HIV RNA viral load: undetectable. From the examination of Thyroglobulin Antibody (TBG-Ab): 40 IU/mL, Thyrotropin Receptor Antibody (TRAb): 61.3 IU/mL.

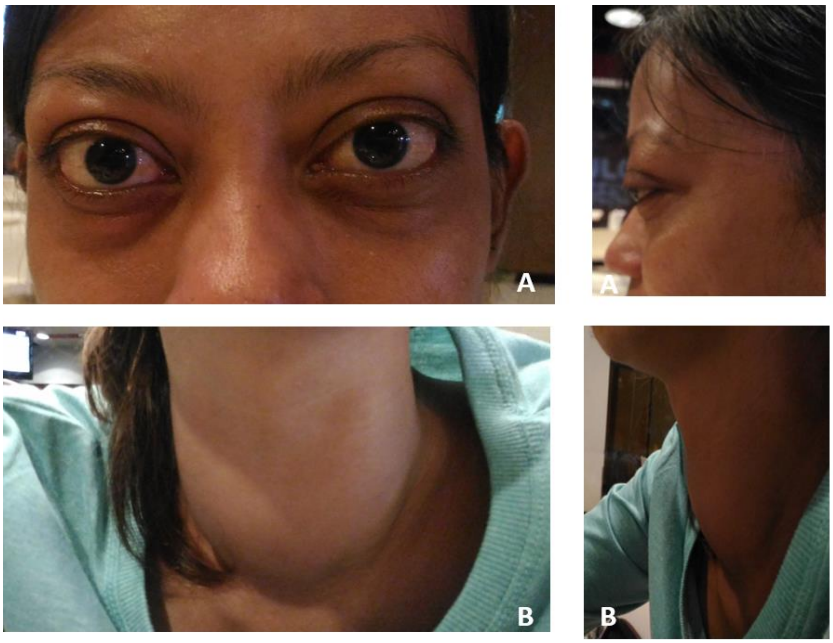

Figure 1. A. Grave's ophtalopathy, B. a diffuse enlargement of thyroid gland.

The patient has received anti-thyroid medication: methimazole, propranolol, and ART: zidovudine, lamivudine, and efavirenz, but after a year, the ART has been substituted into a fixed drug combination (FDC) ART regimen: Tenofovir, Lamivudine, Efavirenz. Currently, the patient has no complaints related to thyroid disease, but the enlargement of the thyroid gland and GO

has not been resolved. The last record of CD4 levels was 665 cells/µL, FT4 1.14 ng/dL, and TSH 0.19 IU/mL.

After 6 months, the patient experienced frequent vaginal bleeding. After being evaluated by the Obstetrics and Gynecology section, the patient was diagnosed with cervical cancer (Papillary Squamous Cell Carcinoma) stage II A and had completed neoadjuvant chemotherapy paclitaxel + carboplatin 4 series, the last time was given on March 21, 2021, and is scheduled to run radiotherapy. In 2022, patients will continue to consume ARVs and anti-thyroid drugs regularly and have been hospitalized several times due to vaginal bleeding and receiving red blood cell transfusion therapy.

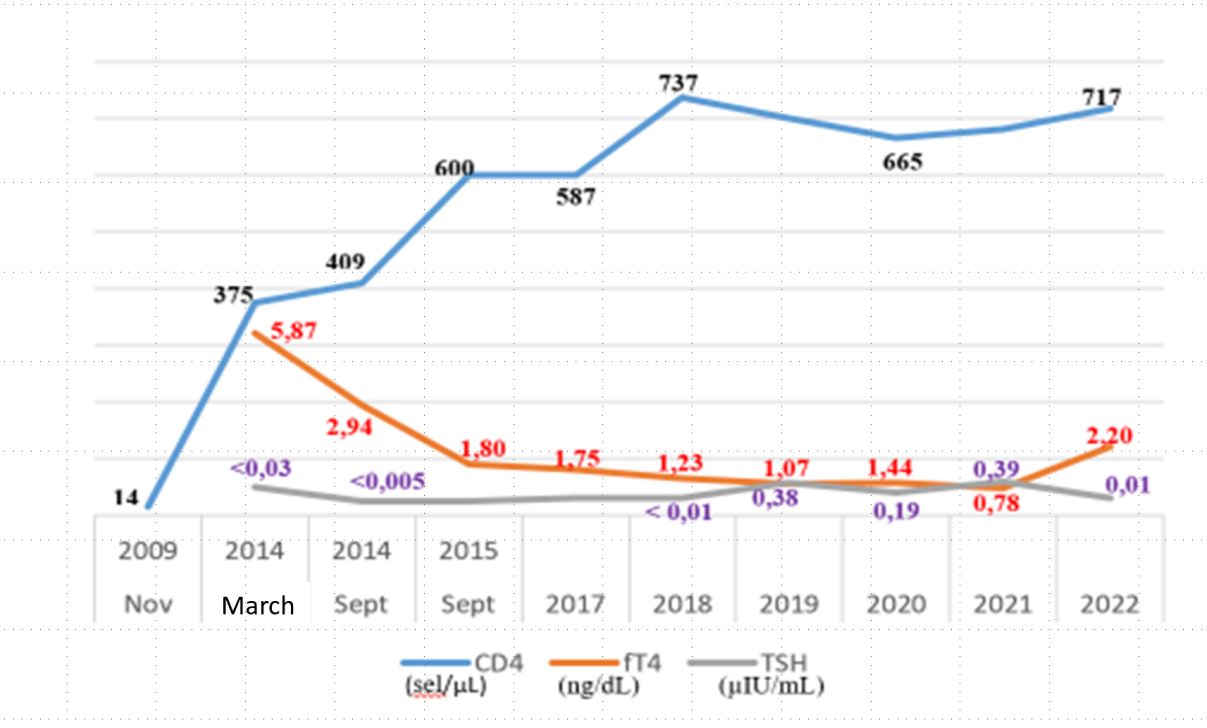

Figure 2. Graphic of CD4 levels and thyroid function test from the patient.

DISCUSSION

The efforts to control HIV have shown encouraging results. Experts predict that by 2030 HIV infection will no longer be an important health problem. The success of these efforts is inseparable from the guidelines of the Joint United Nations Program on HIV/AIDS (UNAIDS) and WHO as well as international cooperation. However, the number of HIV cases in Indonesia appears to have increased from 7,000 in 2006 to 48,000 in 2017. However, the annual mortality rate for people living with HIV significantly decreased in 2006 from 11% to 0.46% in 2018.8 This shows success fast-track approach by all parties, following the objectives of achieving sustainable development goals (SDGs).[6,7]

Behind the success of ART in reducing morbidity and mortality of people living with HIV-AIDS.[8] Improvements and increases in CD4 levels that indicate recovery of the immune system in HIV-AIDS patients receiving ART can also indicate a phenomenon known as Immune Reconstruction Syndrome (IRIS). IRIS is a clinical condition worsening due to an exaggerated inflammatory response during recovery of the immune response after ART administration. IRIS manifestations can be either infectious or non-infectious.[9,10] According to the International Network Study of HIV-associated IRIS (NISH), the diagnostic criteria for IRIS include:

1. Demonstrated response to ART therapy by:

a. Receiving ART
b. Viral load reduction > 1 log copy/mL (if available)
2. Worsening of clinical signs of infection or development of an inflammatory reaction associated with ART initiation
3. The clinical symptoms are not caused by:
a. Clinical symptoms of previously known infections that have been successfully cured
b. Side effects or drug toxicity
c. Therapy failure
d. Non-compliance with ART

Grave's disease has been reported in several works of literature as a manifestation of IRIS in HIV patients who have received ART. In Grave's Disease, autoantibodies are formed against the TSH receptor, so the thyroid gland is activated and produces excess thyroid hormone (hyperthyroidism). In HIV patients, the endocrine glands also experience disturbances, either organ damage or endocrine function; this is related to the HIV itself and subsequent immunosuppressive conditions, the effects of opportunistic infections, both acute and chronic, the effects of HIV-related malignancies, and the treatment used, both ART. or drugs for opportunistic infections. Disruption of the competent immune system is characterized by dysregulation of T cells, where CD8 is more dominant. As a result of T cell dysregulation, "molecular mimicry" is formed, which is the basis for the mechanism of autoimmune disease in HIV. Symptoms and clinical IRIS grave's disease appear together with the immunological improvement of HIV patients who have received ART, and an increase in the CD4 count will be found.[6] Administration of ART showed an increase in CD4 cells from 14 cells/µL to 375 cells/µL, and TRab+ autoantibodies were detected. In some literature, it is described that the appearance of symptoms and signs of GD range from 8-33 months after the use of ART.[4,12]

Grave's IRIS was first published by Gilquin et al. in 1998 in the form of 3 case reports.13 Since it was first published, only a few cases have been reported.[13-15] In this case, the initial CD4 cell/L was 14 cells/L, and when GD was established, the CD4 was 375 cells/µL. . Grave's IRIS appears in patients with an initial CD4 of less than 100 cells/µL. According to the case study by Samad et al., the mean initial CD4 of patients with Grave's IRIS was 59 cells/µL (29-89 cells/µL), and an average CD4 cell count of 59 cells/L (29-89 cells/µL). The average increase in CD4 cells when symptoms of Grave's IRIS appeared was 357 cells/µL (191-448 cells/µL). None of the patients in this case study had a previous history of impaired thyroid function.[16] As in the case, there was no previous history of thyroid dysfunction, and after receiving ART, they showed GD symptoms with increased fT4, suppressed TSH, and TRAb+ with elevated CD4 cells. So it can be estimated that the patient in the case showed manifestations of Grave's IRIS.

The role of ART in the incidence of GD is uncertain. Most experts state that GD is the result of the immune reconstruction process that occurs. Some studies suggest that ART will affect thyroid function and hypothyroidism associated with protease inhibitor regimens. Meanwhile, hyperthyroidism is associated with non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially efavirenz.[16,17] Although patients are using the efavirenz regimen, the use of ARV drugs as a direct cause of GD has not been determined. While GD therapy as a manifestation of IRIS in HIV is the same as GD therapy in general, with oral anti-thyroid treatment, beta-blockers, and symptomatic drugs, if the therapeutic response is not achieved, active iodine radiation therapy or surgery can be selected.[18]

In the case of patients who have been diagnosed with HIV for 11 years and 8 years since the symptoms of Grave's IRIS appeared, ART and thyroid drugs are always taken regularly. However, new complaints emerged from abnormal vaginal

bleeding and finally diagnosed with cervical cancer (Papillary Squamous Cell Carcinoma) stage II A. According to WHO data, women diagnosed with HIV have a 4-6 times higher risk of cervical cancer than those not infected with HIV. The incidence of cervical cancer, in this case, is related to the duration of HIV infection itself or what is the role of IRIS in causing immune system dysregulation that causes the autoimmune disease is still difficult to ascertain. The explanation by Elkoshi, 2022 states that prolonged inflammatory conditions and levels (high or low) of reactive oxygen species (ROS) in autoimmune diseases play a role in cancer incidence. The high and low levels (ROS) effects on cancer reflect the effects on autoimmune diseases. Cancer is optimally induced by moderately high (intermediate) ROS levels, while low or very high ROS levels induce autoimmune diseases. On the other hand, at sufficiently high levels of ROS, autoimmune diseases are attenuated. In contrast, very high and very low levels of ROS are cytotoxic and increase cancer incidence.[19]

SUMMARY

IRIS is an immune recovery syndrome in HIV patients who have received antiretroviral therapy, where the emergence of an autoimmune condition is one of the consequences. Prolonged inflammation due to HIV infection and immune dysregulation due to autoimmune as a manifestation of IRIS can be the beginning of the emergence of cancer in HIV patients.

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