

Graves' Disease as an Immune Reconstitution Syndrome in an HIV-1-Positive Patient Commencing Effective Antiretroviral Therapy: Case Report and Literature Review

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ABSTRACT

Combination antiretroviral therapy (cART) reduces morbidity and mortality in human immunodeficiency virus (HIV) infection, but it may also alter the clinical course of subclinical opportunistic infections and can even induce autoimmune disease. These atypical presentations are known as immune restoration disease (IRD), immune reconstitution syndrome/immune recovery syndrome (IRS), or immune restoration inflammatory syndrome (IRIS). We report the case of a 27-year-old, HIV-1-positive woman who developed hyperthyroidism attributable to Graves' disease (GD) after commencing potent cART. At the initiation of cART, her CD4 T cell count was 15 cells/ μ L and plasma HIV RNA 35 000 copies/mL. Her commencement of cART resulted in complete viral suppression and subsequent improvement of the CD4 T-cell count. Three years later, the diagnosis of GD was established based on a typical clinical picture and the results of hormonal and immunological analyses. It coincided with a 58-fold rise of the CD4 T cells. Retrospective analysis of serum samples revealed normal thyroid function and lack of anti-thyroid peroxidase (anti-TPO), anti-thyroid-stimulating hormone receptor (anti-TSHR), and anti-thyroglobulin (anti-TG) autoantibodies at the beginning of cART. HLA class II gene examination did not reveal susceptibility for the GD development in this patient. We suggest that GD in our patient was an IRD, and advise this as a possible differential diagnosis in patients presenting with hyperthyroidism on cART. To provide further details relevant to this case, we also review the literature concerning IRD-GD.

INTRODUCTION

COMBINATION ANTIRETROVIRAL THERAPY (cART) reduces morbidity and mortality in persons with human immunodeficiency virus-1 (HIV-1) infection (16). However, after treatment is commenced, some patients experience clinical deterioration caused by restoration of their capacity to mount an inflammatory immune re-

sponse against both infectious and noninfectious antigens (5,6,22,23). This has been variously known as immune restoration disease (IRD), immune reconstitution syndrome/immune recovery syndrome (IRS), or immune restoration inflammatory syndrome (IRIS) (5).

Autoimmunity as a consequence of IRD may reflect a newly recognized adverse events in HIV-1-positive patients. The development of autoimmune diseases has been

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TABLE 1. SELECTED IMMUNOLOGICAL AND VIROLOGICAL PARAMETERS DURING THE CLINICAL COURSE

Parameter	Time (month year)										
	Apr 2001	Jun 2001	Oct 2001	Apr 2002	Nov 2002	Jul 2003	Oct 2003	Jan 2004	Apr 2004	Dec 2004	May 2005
CD4 T (cells/ μ L)	15	95	140	343	387	462	514	862	618	720	623
HIV RNA (copies/mL)	35000	<50	<50	<50	<50	<50	<50	<50	<50	<50	<50

described mainly as case reports (Graves' disease, alopecia universalis, rheumatoid arthritis) (6,9,12,21,26) and only rarely in cohort studies (2). The pathogenic mechanisms are poorly understood, although awareness of these diseases is important from a clinical perspective (1,4,13,17,19).

We report here a case of hyperthyroidism caused by Graves' disease (GD) that developed after a patient commenced cART.

CASE REPORT

The patient was a 27-year-old woman with HIV-1 infection, probably acquired 10 years previously through heterosexual contact. At presentation in March 2001, she had a very low CD4 T-cell count (12 cells/ μ L). The patient denied any previous opportunistic infections. Physical examination revealed only thrush, but no other symptoms of immune deficiency were observed. The patient received cART consisting of stavudine, lamivudine, amprenavir, and ritonavir. The therapy quickly suppressed viral replication, and a significant rise of the CD4 T cell

count followed. Selected parameters concerning the clinical course are presented in Tables 1 and 2.

At presentation, the patient had no signs or symptoms of thyroid dysfunction. Her body mass was 67 kg and her height 158 cm. She reported having smoked ~20 cigarettes daily for 10 years. Normal thyroid function (TSH, fT₃, fT₄ levels) and lack of autoantibodies (anti-thyroid peroxidase [anti-TPO], anti-TSH receptor [anti-TSHR], and anti-thyroglobulin [anti-TG]) were documented retrospectively by appropriate laboratory tests. There was no past personal or family history regarding thyroid disease. The results of hormonal analyses and thyroid autoantibodies carried out at the presentation (March 2001), thyrotoxicosis diagnosis (April 2004), and at the time of this report (May 2005) are shown in Table 2. HLA class II genes subtyping revealed the following result: DRB1*01,*13; DQB1*05*03 indicating no susceptibility for GD development.

Three years after commencing cART, typical signs and symptoms of hyperthyroidism developed (7 kg of weight loss over a 6-month period, heart palpitations, hand tremors, increased frequency of defecation, enlarged thyroid gland, and mild palpebral retraction). These symp-

TABLE 2. THE RESULTS OF HORMONAL ANALYSES AND THYROID ANTIBODIES OF THE PATIENT WITH HIV COMPLICATED BY HYPERTHYROIDISM

Analysis (units)	Onset (Mar 2001)	Hyperthyroid (Apr 2004)	Present (May 2005)	Normal range
Hormones				
TSH (U/L)	1.429	<0.03	0.03	0.49–4.67
FT4 (pmol/L)	11.2	33.41	23.75	9.11–23.81
FT3 (pmol/L)	2.5			2.2–5.8
Autoantibodies				
Anti-TPO (U/mL)	10	—	178	<50
Anti-TG (U/mL)	20	—	21	<100
Anti-TSHR (U/mL)	<1	—	11.3	<2

TSH, thyroid-stimulating hormone; Anti-TPO, anti-thyroid peroxidase; Anti-TG, antithyroglobulin; Anti-TSHR, anti-thyroid-stimulating hormone receptor; FT4, free thyroxine; FT3, free triiodothyronine.

toms were associated with suppressed TSH and elevated free thyroxine (fT₄) concentrations (Table 2). Neither ultrasound examination nor iodine uptake measurement were carried out at the time that hyperthyroidism was diagnosed. Anti-thyroid therapy with propylthiouracil (100 mg t.i.d. with a subsequent gradual dose reduction) and β -blocker therapy with propranolol (10 mg t.i.d.) was commenced. The thyroid function normalized clinically 6 weeks after the treatment was initiated. In November 2004, recurrence of hyperthyroidism was noticed, and medication was changed to methimazole (5 mg t.i.d.). At present, there are no signs or symptoms of thyroid dysfunction, palpebral retraction has resolved, the thyroid has decreased in size, and hormonal results are normal. The patient is taking methimazole (5 mg q.d.) as maintenance anti-thyroid therapy. The elevated levels of anti-TSHR and anti-TPO autoantibodies (Table 2) has persisted. The thyroid gland is slightly enlarged (22 cm³) on ultrasound examination, with a nonhomogenous echostructure caused by numerous hypoechogenic noduli 2–4 mm in diameter, probably resulting from long-term anti-thyroid therapy.

Neither diffuse goiter nor severe ophthalmopathy, apart from a mild palpebral retraction, were present during the course of the thyroid dysfunction. Anti-thyroid therapy led to cessation of symptoms and to normalization of thyroid function. Maintenance anti-thyroid therapy is foreseen for the next 6–12 months.

LITERATURE REVIEW AND DISCUSSION

We report a case of hyperthyroidism caused by Graves' disease after commencing potent cART. Thyroid dysfunction is not common in HIV-1 positive patients and the number of reports on IRD-GD as a result of cART is scanty compared with other IRDs (3,5,7,22,23). However, our case illustrates that GD is a potential adverse event in patients commencing cART.

Immune reconstitution. Treatment with cART suppresses viral replication, allowing the immune function to recover, demonstrated by an increase in the number of CD4 T cells within the first few months of therapy (1). The CD4 T cells are mainly of memory phenotype caused by redistribution from the lymphoid tissue into the circulation. This is followed by a slower but continuous increase, lasting months to years, of naive CD4 T cells of thymic origin. Most researchers suggest a link between suppression of HIV-1 replication as a consequence of cART, increased thymic output of naive cells, and greater thymic size (4,19,20). Poor CD4 T-cell increases observed in some patients with good virological response to cART may be caused by the failure of thymic T-cell production (24).

It is well known that T cells undergo both negative and positive selection in the thymus. Only cells capable of recognizing major histocompatibility complex molecules complexed with foreign antigens and unable to react with self-antigens enter the periphery. The remaining cells undergo apoptosis, or programmed cell death (9,12,14,26). It has been suggested that, as a result of these immunological events, intense regeneration of the thymus upon cART may lead to the failure to delete autoreactive T cell clones, abnormally high numbers of thymus-derived T cells in the blood, and development of GD-IRD (9,12).

An increasing number of reports have described IRD caused by opportunistic infections (3,5,7,17,22,23). Descriptions of diseases caused by the inflammatory response to noninfectious immunogenic antigens are less common (2,6,9,12,21). Autoimmune diseases such as IRD may develop after cART for the first time, or pre-existing diseases may be exacerbated by cART. Some of them (lupus erythematosus, polymyositis, rheumatoid arthritis) manifest within a few months after the onset of cART (26). GD develops after a longer period than other autoimmune diseases in patients receiving cART (12–32 months), and, as mentioned above, is caused by thymic dysfunction during immune reconstitution (6,7,12,21,22).

Moreover, certain predisposing factors such as the extent and duration of the immune deficiency, velocity of immune reconstitution, high-fold increase in CD4 T lymphocytes, as well as genetic susceptibility (polymorphism in cytokine genes of interleukin [IL]-6, IL-12, and tumor necrosis factor- α (TNF- α) enhance the risk of IRD development (3,18,23).

Hormonal dysfunction in HIV-positive patients. In HIV patients, thyroid dysfunction is not common compared with gonadal dysfunction, lipodystrophy, hyperglycemia, electrolytes imbalance, and adrenal insufficiency. Subclinical alterations in thyroid tests are more commonly observed than clinically overt disease. Hypothyroidism with anti-TPO antibodies has been reported in adults, whereas hyperthyroidism with anti-TG antibodies has been seen in HIV infected children (8,15). There are reports of increased thyroid-binding globulin (TBG) levels in patients with AIDS, and these levels correlated inversely with CD4 T-cell counts; but the clinical significance of this change is unclear. Other phenomena could be decreased T₃ and RT₃ levels (10). In the case of opportunistic infections such as *Pneumocystis carinii* (jiroveci) infection, a painful thyroiditis-like condition with hyperthyroidism followed by hypothyroidism may be observed (10).

On the other hand, there are only several reports concerning GD-IRD development after immune reconstitution caused by cART (2,6,9,12,21,22,23).

Graves' disease after immune restoration. Gilquin et al. reported delayed occurrence of GD in three patients after immune restoration with cART. The median rise of the CD4 T cells was 187 cells/ μ L and the time from initiating cART to GD development was 18 months (9). Jubault et al. observed thyroid-specific autoimmunity upon immune restoration with highly active antiretroviral therapy in five HIV-1-positive, severely immunocompromised patients. None of the patients had a personal or family history of thyroid or autoimmune disease or had been given drugs known to interfere with thyroid function. Autoantibodies were absent before immune restoration. Thus, the exacerbation of pre-existing thyroid autoimmune disease was excluded. The patients developed delayed GD 14–22 months (median 20 months) after cART commencement and 12–19 months (median 18 months) after CD4 T cell rise (12). The appearance of anti-TPO and anti-TSHR antibodies followed significant CD4 T cell rise, and the GD manifestation was associated with an increase of anti-TSHR antibody levels (12). Shelburne et al. described one case of GD-IRD in a 46-year-old man receiving cART with advanced immune deficiency (120 cells/ μ L). Ten months after commencement of cART he developed GD, which was confirmed by T₃, T₄, and TSH levels as well as by increased radioactive iodine uptake (22). Sereti et al. presented a report of a 30-year-old, HIV-1-positive man with advanced immune deficiency who developed a dramatic immediate rise of CD4 T cells because of viral suppression as a result of cART. After 4 months of effective antiretroviral therapy, alopecia universalis accompanied by subclinical hypothyroidism was observed. Follow-up testing showed spontaneous resolution of the hypothyroidism. Nine months after initiating cART, a new regimen was commenced because of virological failure. This resulted in GD development within the next 10 months of potent cART (21).

Finally, Chen et al. presented results of a first cohort study concerning "late" manifestation of autoimmune thyroid disease (AITD) as IRD after effective cART. Seventeen patients were diagnosed with AITD, and in 15 of them GD was diagnosed. The median duration of the immune reconstitution was 17 months. AITD patients were more likely than controls to have advanced immune deficiency at baseline and more pronounced CD4 T cell rise resulting from cART (2).

Our patient had GD, which was diagnosed 36 months after initiating effective cART (Table 1). Both viral suppression and the beginning of the documented rise in CD4 T cells were observed 10 weeks after cART (95 cells/ μ L), followed by a gradual increase in these cells up to 862 cells/ μ L in January 2004; this was almost a 58-fold increase within 33 months, compared with the number of the CD4 T cells tested at the cART initiation. Neither GD

nor family history of thyroid or autoimmune diseases had been reported in our patient before the introduction of cART. There was no history of use of any drug known to interfere with thyroid function. We suggest that GD in our patient was caused by IRD. The time from the significant CD4 T cell rise to GD diagnosis was longer than reported by others (2,9,12,22), although the likely time of initiation of GD in our patient was several months before the time, as evidenced by a history of significant weight loss over a period of at least 6 months, when the diagnosis was made. Only French et al. presented a similar observation of a patient with HIV infection who developed severe GD 32 months after commencing effective cART (6).

The disease was caused by the abnormal restoration of the immune mechanisms as a result of successful antiretroviral therapy in the previously untreated patient with advanced immune deficiency. Altered T-cell repertoire, thymic environment disturbances, and immune reconstitution on commencement of cART resulted in the autoimmunity, which was caused by the disruption of peripheral tolerance and unbalanced growth of immunoregulatory and autoreactive components (4,6,9,13,22).

The role of HLA polymorphism in the clinical expression of GD has been explored (25). Among persons of white ethnicity HLA-DR3 (HLA-DRB1*03) and HLA-DQA1*0501 were shown to be associated with GD (25). We subtyped HLA-DRB1*01,*13; DQB1*05*03 in our patient, indicating that no HLA susceptibility alleles in GD were found. No data concerning susceptibility allele in GD-IRD are available.

Our report describes one more emergence of IRD—an unexpected manifestation of GD as a result of potent cART—and is consistent with the previous reports. One should therefore expect its occurrence in any case of hyperthyroidism after effective antiretroviral therapy in HIV-1-positive individuals, even 2–3 years after commencement of therapy.

All of the cases reported present a few features in common. The patients had, at baseline, profound immune deficiency. There were rapid and large increases of the CD4 T-cell count as a result of potent cART. The onset of IRD-GD among published cases was between 12 and 32 months after starting cART. GD-IRD developed after a long period, while the patients were in good condition and while complications resulting from cART were expected. No features of any autoimmune diseases were diagnosed before antiretroviral therapy was initiated. Clinicians should be aware of the possibility of GD-IRD in any case of hyperthyroidism in an HIV-1-positive individual after a few months of effective antiretroviral therapy followed by viral suppression and significant immune restoration.

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