Sequential Occurrence of Thyroid Autoantibodies and Graves' Disease after Immune Restoration in Severely Immunocompromised Human Immunodeficiency Virus-1-Infected Patients

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Progression of autoimmune thyroiditis in an HIV-infected woman on HAART.

Rosenfeld CR, **Calabrese LH**.

Changes in immunoregulation, among other factors, may initiate or exacerbate autoimmune thyroiditis. Strikingly high titers of antithyroid peroxidase antibodies have been found in HIV-infected patients, and, according to some studies, these increase further as HIV disease progresses. The pathogenesis of autoimmune thyroiditis is not totally understood, but activated CD4+ cells predominate in the infiltrate and are believed to be central to the process. Some investigators have postulated that endocrinologic autoimmunity might result from incomplete or unbalanced immune restoration with highly active antiretroviral therapy (HAART). The case presented here suggests progression from euthyroid Hashimoto's thyroiditis to hypothyroidism after initiation of HAART.

HIV and autoimmunity.

Zandman-Goddard G, **Shoenfeld Y**.

The association of immune dysfunction in patients with human immunodeficiency virus (HIV) infection and AIDS and the development of autoimmune diseases is intriguing. Yet, the spectrum of reported autoimmune phenomena in these patients is increasing. An infectious trigger for immune activation is one of the postulated mechanisms and derives from molecular mimicry. During frank loss of immunocompetence, autoimmune diseases that are predominantly T cell subtype CD8 driven predominate. There is evidence for B cell stimulation and many autoantibodies are reported in HIV patients. We propose a staging of autoimmune manifestations related to HIV/AIDS manifestations and the total CD4 count and viral load that may be beneficial in identifying the type of autoimmune disease and establishing the proper therapy. In stage I there is the acute HIV infection, and the immune system is intact. In this stage, autoimmune diseases may develop. Stage II describes the quiescent period without overt manifestations of AIDS. However, there is a declining CD4 count indicative of some immunosuppression. Autoimmune diseases are not found. During stage III there is immunosuppression with a low CD4 count and the development of AIDS. CD8 T cells predominant and diseases such as psoriasis and diffuse immune lymphocytic syndrome (similar to Sjogren's syndrome) may present or even be the initial manifestation of AIDS. Also during this stage no autoimmune diseases are found. In stage IV there is restoration of immune competence following highly active anti-retroviral therapy (HAART). In this setting, there is a resurgence of autoimmune diseases. The frequency of reported rheumatological syndromes in HIV-infected patients ranges from 1 to 60%. The list of reported autoimmune diseases in HIV/AIDS include systemic lupus erythematosus, anti-phospholipid syndrome, vasculitis, primary biliary cirrhosis, polymyosits, Graves' disease, and idiopathic thrombocytopenic purpura. Also, there is an array of autoantibodies reported in

HIV/AIDS patients which include anti-cardiolipin, anti-beta2 GPI, anti-DNA, anti-small nuclear ribonucleoproteins (snRNP), anti-thyroglobulin, anti-thyroid peroxidase, anti-myosin, and anti-erythropoietin antibodies. The association of autoantibodies in HIV-infected patients to clinical autoimmune disease is yet to be established. With the upsurge of HAART, the incidence of autoimmune diseases in HIV-infected patients is increasing. In this review, we describe the various autoimmune diseases that develop in HIV/AIDS patients through possible mechanisms related to immune activation.

Graves' disease during immune reconstitution after highly active antiretroviral therapy for HIV infection: evidence of thymic dysfunction.

French MA, Lewin SR, Dykstra C, Krueger R, Price P, Leedman PJ.

A patient with HIV infection who experienced immune reconstitution after highly active antiretroviral therapy (HAART) [increase in CD4 T cell count from <1/microl to >600/microl] presented with severe Graves' disease 32 months after commencing HAART. A comprehensive clinical and laboratory study demonstrated pronounced regional lymphadenopathy and thymic enlargement at presentation, and that the onset of thyrotropin receptor antibody production was associated with increased production of soluble CD30 (a marker of type 2 immune responses). Blood naive CD8 T cell counts and TREC levels in both CD4 and CD8 T cells were increased at multiple time points compared with carefully selected controls. We conclude that the Graves' disease in this patient was associated with abnormally high blood counts of thymus-derived T cells, and propose that Graves' disease after HAART in this and other HIV patients may result from failure to delete autoreactive T cell clones in the regenerating thymus.

Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease.

Chen F, Day SL, Metcalfe RA, Sethi G, Kapembwa MS, Brook MG, Churchill D, de Ruiter A, Robinson S, Lacey CJ, Weetman AP.

Experimental evidence from animal models has provided a framework for our current understanding of autoimmune disease pathogenesis and supports the importance of genetic predisposition, molecular mimicry, and immune dysregulation. However, only recently has evidence emerged to support the role of immune dysregulation in human organ-specific autoimmune disease. In the current study of the "late" manifestation of autoimmune thyroid disease (AITD) in a cohort of human immunodeficiency virus (HIV)-positive patients following highly active antiretroviral therapy (HAART), we discuss how immune dysregulation and factors associated with the immunopathology of HIV infection fit the current understanding of autoimmunity and provide a plausible basis for our clinical observations. De novo diagnoses of thyroid disease were identified between 1996 and 2002 in 7 HIV treatment centers (5/7 centers completed the study). Patients were diagnosed as clinical case entities and not discovered through thyroid function test screening. Paired plasma specimens were used to demonstrate sequential rise in thyroid antibodies.Seventeen patients were diagnosed with AITD (median age, 38 yr; 65% were of black African or black Caribbean ethnicity; and 82% were female). The median duration of immune reconstitution was 17 months. Graves disease (GD) was diagnosed in 15 of 17 patients. One patient developed hashithyrotoxicosis with atypically raised C-reactive protein, and another developed hypothyroidism. One GD patient had associated secondary hypoadrenalism. The

estimated combined prevalence of GD for 4 treatment centers for female patients was 7/234 and for males was 2/1289. The denominator numbers were matched controls, from 4 centers able to provide data, who commenced HAART during the same time (January 1996 to July 2002) and who did not develop clinical AITD. The mean baseline pre-HAART CD4 count was 67 cells/mL, and the mean increase from nadir to AITD presentation was 355 cells/mL. AITD patients were more likely than controls (95% confidence interval, chi-square test) to be severely compromised at baseline (as defined by a CD4 count < 200 cells/mL or the presence of an acquired immunodeficiency syndrome [AIDS]-defining diagnosis), and to experience greater CD4 increments following HAART. AITD may be a late manifestation of immune reconstitution in HIV-positive patients taking HAART, and immune dysregulation may be an important factor.

Rheumatic complications of human immunodeficiency virus infection in the era of highly active antiretroviral therapy: emergence of a new syndrome of immune reconstitution and changing patterns of disease.

Calabrese LH, Kirchner E, Shrestha R.

OBJECTIVE: To describe the impact of the introduction of highly active antiretroviral therapy (HAART) on the nature and frequency of rheumatic complications in human immunodeficiency virus (HIV)-infected patients. METHODS: Case report and systematic review of a newly described syndrome of rheumatic immune reconstitution syndrome and prospective longitudinal cohort study analyzing the frequency and nature of rheumatic complications in the setting of HIV infection from 1989 through 2000. RESULTS: A newly described syndrome of either the de novo appearance or the exacerbation of clinically occult autoimmunity following immune reconstitution from HAART is described. Including the present case report, 32 cases have been individually described with sarcoidosis and autoimmune thyroid disease being most common with arthritis and various forms of connective tissue disease making up the rest. The mean onset to their appearance following HAART was nearly 9 months and most resolved with little or no therapy. In addition, a longitudinal analysis of 395 HIV-infected patients from 1989 to 2000 designed to detect the appearance of rheumatic complications has revealed a dramatic decline in certain problems such as reactive arthritis, psoriatic arthritis, and various forms of connective tissue disease. New rheumatic complications possibly due to the effects of longer survival and metabolic derangements associated with this form of therapy are now being described and may become more formidable problems in this population in the future. CONCLUSIONS: HAART has had a profound beneficial effect on survival in HIV-infected patients but has also contributed to both an altered frequency and a different nature of rheumatic complications now being observed in this population. Rheumatologists need to be aware of these changes to provide optimal diagnosis and treatment for this group.

Subclinical hypothyroidism in HIV-infected patients is not an autoimmune disease.

Beltran S, Lescure FX, El Esper I, Schmit JL, Desailloud R.

AIMS AND METHODS: A study of 350 HIV+ patients in our region showed that 16% suffered from hypothyroidism. Twenty-two HIV+ hypothyroid patients (10 with subclinical hypothyroidism, 12 with low FT4 levels (LT4) (confirmed by a dialysis equilibrium assay) and 22 HIV+ euthyroid controls receiving highly active anti-retroviral therapy were included in an additional study. RESULTS: No goiter or anti-thyroid antibodies were detected. Use of stavudine was more frequent in the LT4 subgroup ($p < 0.01$) and subclinical hypothyroidism

group (p = 0.04). Use of didanosine (OR, 12.5, p < 0.01) and ritonavir (OR, 33.0, p < 0.01) was more frequent in the LT4 subgroup, with a greater didanosine cumulative dose (616.7 mg [180.0, 1,260.0] vs. 263.7 [63.0, 948.0], p = 0.01). Reverse T3, binding protein levels, the TSH response to thyrotropin-releasing hormone, urinary iodine, plasma selenium and thiocyanate levels did not differ. IFNgamma levels were lower in the subclinical hypothyroidism group (pg/ml) (9.1 [0.0, 22.7] vs. 19.5 [0.0, 40.9], p = 0.03). CONCLUSION: None of the investigated mechanisms are able to explain the occurrence of hypothyroidism in HIV patients receiving highly active anti-retroviral therapy except the anti-retroviral treatment. In light of the absence of autoimmunity, the normal adenohypophysis and thyroid responses to thyrotropin-releasing hormone, central hypothyroidism is suspected and could explain LT4 and high TSH levels. Underlying mechanisms need further exploration.

Thyrotoxic periodic paralysis in a Polynesian male following highly active antiretroviral therapy for HIV infection.

Brown JD, **Kangwanprasert M**, **Tice A**, **Melish J**.

Hyperthyroidism has been described after highly active antiretroviral therapy for AIDS and has been attributed to late onset immune reconstitution. The team reports a young Polynesian man with AIDS who responded to highly active antiretroviraltherapy. However, 15 months after initiation of antiretroviral therapy, he was hospitalized for hypokalemic thyrotoxic periodic paralysis, an unusual manifestation of hyperthyroidism which typically occurs in young Asian males.