

IFN α -Induced Recurrence of Graves' Disease Ten Years after Thyroidectomy in Chronic Viral Hepatitis C. Case Report

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Abstract

In contrast to chronic or subacute thyroiditis, Graves' disease rarely complicates IFN- α therapy for chronic viral C hepatitis. We report the case of a 51-year-old man in whom IFN- α treatment was followed by recurrence of Graves' disease 10 years after thyroidectomy was performed and the patient was declared cured. Despite severe thyrotoxicosis, combined IFN- α and ribavirin therapy was continued and radioiodine treatment was considered for Graves' disease.

Key words

Autoimmune thyroid disease – chronic hepatitis C – alpha-IFN – radioiodine therapy.

Introduction

Epidemiological studies have shown an increased prevalence of autoimmune thyroid disease in patients presenting various digestive disorders with autoimmune features such as celiac disease [1-3], Crohn's disease [4, 5], ulcerative colitis [6], primary biliary cirrhosis [7, 8], autoimmune hepatitis [9] or chronic viral C hepatitis. Increased plasma titers of anti-thyroid (anti-thyroglobuline – anti-Tg and anti-thyroidperoxidase – anti-TPO) antibodies without changes in thyroid hormone levels were reported in patients with chronic viral C hepatitis but not hepatitis B [10]. Conversely, the prevalence of hepatitis C virus antibodies appears to be significantly higher in subjects with autoimmune thyroid disease (11% of patients) in comparison to patients with euthyroid multinodular goiter (2.3% of patients) [11]. The use of interferon (IFN) as a therapeutic measure in chronic hepatitis C further complicates the

relationship between viral liver diseases and thyroid diseases, as revealed by the observations that recombinant IFN- α and - γ administration is associated with autoimmune thyroid disease [12]. In line with these observations, it has been evidenced that subjects with sub-clinical thyroid dysfunctions and/or high titers of anti-thyroid antibodies at baseline are prone to develop overt thyroid disease during therapy with IFN [13].

We present the case of a patient with chronic hepatitis C in whom thyroidectomy was performed 10 years ago for Graves' disease and rendered him euthyroid and who developed autoimmune thyrotoxicosis during combined IFN- α and ribavirin treatment. Radioiodine cure of thyrotoxicosis was performed without discontinuation of hepatitis C anti-viral therapy.

Case report

A 51-year-old male patient diagnosed with chronic viral C hepatitis, undergoing IFN- α (3 million IU three times weekly) and ribavirin (1g daily) therapy was referred to our outpatient service with clinical features of thyrotoxicosis, mainly weight loss, insomnia, tremor, sweating, nervousness and tachycardia. Ten years ago he presented with a medical history of thyrotoxicosis, diffuse goiter and minor ophthalmopathy. At that time he was diagnosed with Graves' disease and subtotal thyroidectomy was performed. No further therapy has been required since and thyroid function evaluation before therapy with IFN and ribavirin revealed an euthyroid state. Three months after starting antiviral therapy, the patient presented with signs of thyrotoxicosis, elevated serum free T4 (40.4 pg/ml, normal values 6.2-23.3 pg/ml) levels and suppressed thyrotropin (TSH) levels (0 mU/l, normal values 0.3-3.5 mU/l). Thyroid ultrasonography revealed an increased thyroid volume and a diffuse hypoechoic texture of the thyroid gland, with increased radioiodine uptake, of 51% at 2h and 80% at 24h. Doppler ultrasound evaluation of the thyroid showed a diffusely enhanced thyroid blood flow. In addition, high anti-TPO antibodies titers (>1000 U/ml, normal values <35 U/ml) and high anti-TSH receptor antibodies titers (4.1 U/l,

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normal values <1.0 U/l) were detected. Therapy with 15mg/d thiamazol was administered, followed by radioiodine (5 mCi) without discontinuation of anti-viral therapy. Tests of hepatic function were monitored and showed significantly improved values after anti-thyroid therapy was started. Six months after completing anti-viral therapy, dual X-ray absorptiometry (DXA) evaluation revealed low bone mass with a lumbar spine T-score of -3.1 SD, femoral neck T-score of -1.8 SD, Wards triangle T-score of -2.7 SD and a total hip T-score of -1.2 SD and according to the diagnosis criteria of the International Society of Clinical Densitometry (ISCD) [14], our patient was diagnosed with secondary osteoporosis and alendronate therapy once-weekly was started.

Although the patient declined the reevaluation of liver histology, three years after antiviral combination treatment tests of hepatic function were within normal values and stable. At the present time, the patient is free of symptoms, on substitutive hormone therapy with 50 µg/d L-thyroxin.

Discussion

The prevalence of thyroid disease in IFN- α treated subjects varies largely between studies, ranging between 2.5-31% [15]. Clinical thyroid disease has been reported to develop in about 10-15% of those treated with IFN- α for chronic hepatitis C [16, 17], while the rate of subclinical forms of disease is significantly higher. After IFN, most patients will develop thyroid hypofunction, due to autoimmune or destructive thyroiditis, while true hyperthyroidism is more rarely encountered (Table 1). In some cases, IFN-induced thyroid disease may present as subacute inflammatory thyroiditis [18] or as a biphasic disease characterized by a transitory thyrotoxicosis phase followed by hypothyroidism [19]. Thyrotoxicosis, along with the increased titer of anti-TPO antibodies, the enhanced thyroid flow at Doppler ultrasound and increased radioiodine uptake suggested a recurrence of Graves' disease in our patient; in addition,

high anti-TSH receptor antibodies and anti-TPO levels confirmed the diagnosis. Prospective studies on the dynamics of anti-thyroid antibodies titers in IFN-treated subjects indicate a progressive increase of the antibody level within the first 3-6 months after IFN administration. In agreement with this observation, the onset of thyroid dysfunction after three months of IFN- α and ribavirin in our male patient is highly suggestive of antiviral therapy-induced thyroid disease, given the euthyroid status of the subject at start of medication.

Several studies attempted to characterize potential risk factors for IFN- α -induced thyroid disease, one of the most important represented by latent autoimmune thyroid disorders, characterized by normal thyroid function but increased titers of anti-thyroid antibodies and/or changes of the thyroid pattern at ultrasonography. The onset of thyroid disease may vary from weeks after start of therapy to months after completing antiviral medication. A distinct feature in our patient, not described previously, is the recurrence of autoimmune thyrotoxicosis after a long symptom-free period (10 years) in a subject in whom Graves' disease was declared cured. Long-term follow-up of patients is also needed after anti-viral therapy considering that the dysfunction may solve spontaneously. Carella et al concluded that the level of anti-thyroid antibodies at the end of IFN- α therapy may predict the risk of thyroid disease; thus, absence of anti-thyroid antibodies predicts absence of thyroid disease in following years, while high titers of anti-Tg and anti-TPO antibodies is associated with persistence of thyroid dysfunction after IFN cessation [20].

Recent studies reported the development of other endocrine-specific antibodies in IFN-treated subjects with hepatitis C such as glutamic acid decarboxylase antibodies (GAD65Ab), insulin autoantibodies (IA2/ICA512Ab) or anti-21-hydroxylase antibodies. A study carried out on 62 patients with hepatitis C, treated on average 8.3 months with IFN- α concluded that anti-thyroid antibodies developed

Table I. Characteristics and mechanism of IFN-induced thyroid disease

Clinical form	Mechanism	Investigations	Management
Acute/subacute (silent/painless) thyroiditis	Inflammatory	TSH↓, fT3 n/↑, fT4 n/↑ Radioiodine uptake: ↓↓ US: patchy/diffuse hypoechoic structure with reduced blood flow permanent hypothyroidism may develop	Beta-blockers ± Corticosteroids ± L-thyroxin
Chronic thyroiditis	Autoimmune	TSH↓ /n/↑, fT3 n/↑/↓, fT4 n/↑/↓ Anti-TPO Ab (+++), anti-TG Ab (+++), anti-TSH receptor Ab (exceptionally +) Radioiodine uptake: ↓/↑/n US: patchy/diffuse hypoechoic structure with reduced (thyrotoxicosis), normal or increased blood flow (hypothyroidism)	Beta-blockers ± L-thyroxin
	Cytotoxic	TSH ↓/↑, fT3 n/↑/↓, fT4 n/↑/↓ Radioiodine uptake: ↓↓ US: patchy/diffuse hypoechoic structure with reduced blood flow	Beta-blockers ± Corticosteroids ± L-thyroxin
Graves' disease	Autoimmune	TSH ↓, fT3 n/↑, fT4 n/↑ Anti-TSH receptor AB (+++), anti-TPO Ab (++), anti-Tg Ab (++) Radioiodine uptake: ↑↑ US: diffuse hypoechoic structure with increased blood flow	Thiamazol ± Radioiodine ± Beta-blockers

n=normal; ↓=reduced; ↑=increased.

in 19.4% of patients, while 9.7% patients developed GAD65Ab/IA2Ab and only 4.8%, respectively, had anti-21-hydroxylase antibodies; however, neither diabetes mellitus nor adrenal insufficiency was reported in this group of patients [21]. On the other hand, simultaneous development of diabetes mellitus and hashitoxicosis in a patient treated with pegylated IFN- α for chronic hepatitis C has been described recently [22]. Based on the history and DXA examination we diagnosed osteoporosis in our patient, considered of multifactorial origin, secondary to chronic viral hepatitis [23], thyrotoxicosis and, possibly, IFN and ribavirin therapy [24, 25].

IFN-induced thyroid disease exhibits features from both drug-induced thyrotoxicosis (thyroiditis) and autoimmune thyroid disease. The mechanisms of IFN-induced thyroid disease are complex and not completely clarified yet. First, IFN appears to be responsible for an immune system dysfunction by augmentation of cytotoxicity due to increased response of helper lymphocytes [1] and suppression of helper lymphocytes [2] and increased expression of perforin [26], involved as an effector protein in natural killer T lymphocytes cytotoxicity; thus, thyroid-oriented cytotoxic effects on follicular cells induce a pattern of destructive or inflammatory thyroiditis. A study on mice immunized with porcine thyroglobulin and treated with IFN and TNF α showed a response characterized by lymphocyte infiltration of the thyroid and a histological pattern of destructive thyroiditis [27]. In addition, IFN inhibits B lymphocytes apoptosis by enhanced expression of antiapoptotic factors Bcl-2 and Bcl-xL. This, in conjunction with the fact that hepatitis B virus attachment on CD81 activates B lymphocytes explains the development of (thyroid) stimulatory clones of immunoglobulins in treated hepatitis C patients [28]. Second, direct effects of IFN on thyroid metabolism are suggested by cell culture data and may explain the development of non-immune hypothyroidism in patients undergoing IFN therapy. In thyrocytes cultures, both IFN- α and - β decrease 125 I uptake [29], inhibit the expression of the TSH-induced Na-I symporter and the production of T4 in the culture medium [30]. Moreover, IFN- α and - β decrease the expression of TSH-induced Tg and TPO, thus decreasing thyroid hormone biosynthesis [30]. IFN γ alters the barrier capacity of the thyrocyte membrane, demonstrated by a decreased electrical cell resistance and exposure of thyroid autoantigenes [31].

We propose that the diagnosis of IFN-induced thyroid disease should be based on increased anti-thyroid antibodies levels, thyroid ultrasound aspect with variable changes of thyroid volume or thyroid blood flow and hypoechoic patchy or diffuse pattern, and free triiodothyronine (FT3), FT4 and/or TSH levels showing euthyroidism, sub-clinical or overt thyrotoxicosis or hypothyroidism, respectively. Information on the pathogenic mechanism of IFN-induced thyroid disease may be offered by anti-TSH receptor antibodies, with high titers in Graves' disease, the radioiodine uptake test showing low values in thyroiditis (Table I) and the perchlorate discharge test positive in intrathyroidal defects of iodine organification (suggestive of direct effects of IFN in

the absence of thyroid autoimmunity). Unlike amiodarone-induced thyroiditis, serum interleukin-6 concentrations are not useful in differentiating between patients with thyroiditis and hyperthyroidism induced by IFN [32].

Therapy of IFN-induced thyroid disease varies, in accordance with the type and mechanism of the underlying thyroid dysfunction (Table I). In contrast to thyroid hypofunction, therapy in patients developing thyrotoxicosis is more challenging. In thyroiditis, beta-blocking agents or corticosteroid therapy might be efficacious and usually sufficient. If severe thyrotoxicosis is present, management of the disease is controversial with authors suggesting either cessation or continuation of IFN therapy [33]. Anti-thyroid drugs are needed in patients with Graves' disease but careful follow-up of liver function and the use of low-moderate doses are recommended due to potential adverse effects on liver function.

Radioiodine therapy in cases with normal/increased radioiodine uptake may be of major benefit [34]. Therefore, in our patient, IFN therapy was not discontinued, despite severe thyrotoxicosis. Instead, radioactive iodine therapy was chosen as a definitive method to cure hyperthyroidism and to avoid long-term therapy with thiamazol.

Conflicts of interest

None to declare.

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