CLINICAL STUDY

Interferon- α -induced hyperthyroidism: a three-stage evolution from silent thyroiditis towards Graves' disease

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Abstract

Autoimmune thyroid disease is a common side-effect of interferon- α (IFN- α) treatment of viral hepatitis C. We have described three patients with hepatitis C for whom IFN- α and ribavirin were prescribed and who developed two successive phases of silent thyroiditis followed by hyperthyroidism relapse due to Graves' disease. These three men had no known history of familial or personal thyroid disease. Destructive thyrotoxicosis appeared 4–6 months after starting IFN- α , followed by Graves' hyperthyroidism within 8 to 11 months. The thyrotropin (TSH) level was normal before IFN- α was started. The diagnosis of destructive thyroiditis was confirmed by anti-TSH receptor antibody (TSHRAb) negativity and the absence of radionuclide (¹²³I or ⁹⁹Tc) uptake on thyroid scintiscans. Eight to eleven months after starting treatment, TSHRAb positivity and intense scintigraphic uptake confirmed the appearance of Graves' disease. IFN- α was continued in only one patient. Hence, hyperthyroidism induced by IFN- α could correspond to the first phase of silent thyroiditis, to Graves' disease or to the succession of both. Rigorous diagnostic procedures with repeated scintiscans and TSHRAb titering are necessary to avoid a false diagnosis and inappropriate therapy.

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Introduction

Recombinant interferon- α (IFN- α), alone or in combination, is extensively prescribed to treat hepatitis C. However, its use is not without side-effects, among which is the emergence of autoimmune diseases favored by the immunomodulating properties of this molecule. Autoimmune thyroiditis is the most common of these diseases. It affects 2–19% of IFN- α -treated patients (1), depending on the study and diagnostic criteria applied. Thyroiditis is frequently accompanied by thyroid dysfunction, mostly hypothyroidism and thyrotoxicosis in only a minority of cases (2). The most frequently observed clinical picture is silent thyroiditis, with an initial transient thyrotoxicosis phase associated with decreased radionuclide uptake, followed inconsistently by a phase of hypothyroidism that usually resolves spontaneously. IFN- α -induced Graves' disease is less common. It was not observed in some studies (2, 3), but has been reported by other authors (4, 5).

Herein we describe three patients with chronic hepatitis C treated with IFN- α and who successively

developed typical silent thyroiditis that progressed in two phases: thyrotoxicosis and hypothyroidism followed by Graves' disease. This unusual evolution has not been described previously. In addition to diagnostic and management difficulties, it suggests a new entity to be considered: IFN- α -induced triphasic thyroiditis.

Case reports

Case 1

A 41-year-old man who had been treated with pegylated IFN- α and ribavirin for chronic hepatitis C since October 2003 was referred to us in February 2004. He complained of asthenia, palpitations, 9 kg weight loss and nervousness. Hyperthyroidism was suspected and physical examination detected a painless, firm, non-vascularized small goiter with no palpable nodule or adenopathy. He had no familial or personal history of thyroid dysfunction. The level of thyrotropin (TSH) before starting IFN- α (Schering-Plough, 92307 Levallois-Perret Cedex, France) was normal at

1.9 mIU/l (normal (N): 0.27–4.2 mIU/l). The diagnosis of thyrotoxicosis was confirmed: TSH was 0.01 mIU/l; free tri-iodothyronine (FT3) was 19 ng/l (N: 2.57–4.43 ng/l) and free thyroxine (FT4) was 77 ng/l (N: 9.3–17 ng/l). Anti-thyroid drug (carbimazole, DB Pharma, 94210 La Varenne-St-Hilaire, France) was prescribed and IFN- α was continued (Table 1).

Anti-thyroperoxidase antibodies (TPOAbs) and anti-TSH receptor antibodies (TSHRabs) (TRAK assay; BRAHMS Laboratory, Henningsdorf, Germany) were negative (<1 IU/l; N: <2), anti-thyroglobulin antibodies (TgAbs) were positive (280 IU/ml; N: <130). Cervical ultrasonography confirmed the presence of a homogeneous hypoechogenic goiter (overall thyroid volume 27 ml). ^{99}Tc scintiscan (Fig. 1a) showed no thyroid uptake. All these results were typical of destructive thyrotoxicosis and so carbimazole, which had been taken for a total of 15 days, was stopped and symptomatic therapy with a β -blocker was initiated. Two weeks later, the patient had a normal TSH level (1 mIU/l), but a decreased concentration of FT4 (4.9 ng/l). Fifteen days later, the patient was in frank hypothyroidism: TSH 53 mIU/l and FT4 1.9 ng/ml. L-thyroxine (LT4) (Merke Liphia Sante, 69008 Lyon, France) was started on 15 April, while IFN- α was continued.

In early July, the patient presented with a recurrence of thyrotoxicosis with a corresponding hormone profile (Table 2). LT4 was stopped and a β -blocker was reintroduced. The clinical condition worsened with a loss of 10 kg in 1 month. Simultaneously, FT4 and FT3 had increased to 39 ng/l and 18 ng/l. Prednisolone (Laboratoire Aventis, 75601 Paris 12 Cedex, France) was prescribed (40 mg/day) as previously described in interferon-induced severe destructive thyroiditis (1), while the diagnosis procedure was reinitiated.

Thyroid sonography revealed an unchanged thyroid volume but with hypervascularization of the parenchyma. TPOAbs had become positive (470 IU/ml; N: <130 IU/ml) and the TgAb titer was 462 IU/ml. The TSHRab assay was strongly positive at 34 IU/l (N: <2 IU/l). The ^{99}Tc scintiscan showed an intense diffuse and homogeneous uptake (Fig. 1b) of the tracer. Prednisolone was then stopped and carbimazole (60 mg/day) was started as IFN- α treatment was continued. Thyroid function normalized in 6 weeks. Evolution was unremarkable under treatment.

In September 2004, IFN- α was stopped at the scheduled time and the patient's hepatitis C is currently in remission. The patient is still being treated with anti-thyroid drugs and LT4.

Case 2

A 39-year-old man with hepatitis C started treatment with pegylated IFN- α and ribavarin in September 2002. His initial TSH concentration was normal (1.4 mIU/l). No prior thyroid disease was known. Four months later, routine monitoring demonstrated low TSH (<0.05 mIU/l) (Table 1). A thyroid work-up performed in January 2003 detected a painless goiter of moderate size, normal urinary iodine at 82 $\mu\text{g}/24\text{ h}$, TSH <0.02 mIU/l, FT4 26 ng/l (N: 9.3–17 ng/l) and FT3 8.5 ng/l (N: 2.5–4.4 ng/l), TPOAbs 91 IU/ml (N: <30 IU/ml) and TSHRabs were negative (human TRAK assay) and ultrasonography showed the goiter to be hypoechogenic, without nodules and ^{123}I scintigraphy detected less than 2% uptake (Fig. 1c). No treatment was prescribed for this asymptomatic patient and IFN- α treatment was continued.

Hypothyroidism became evident in late March 2003 with TSH at 50 mIU/l and FT4 at 2.48 ng/l. As the

Table 1 Biphasic thyroiditis in three cases.

Parameter	Case 1	Case 2	Case 3
Year of diagnosis	2004	2003	2004
Sex	Male	Male	Male
First phase of thyroiditis: thyrotoxicosis			
TSH (N: 0.27–4.2 mIU/l)	<0.01	<0.02	<0.01
FT4 (N: 9.3–17 ng/l)	77	26	12.9
FT3 (N: 2.57–4.43 ng/l)	19	8.5	4.6
Months to thyrotoxicosis	4	4	6
TPOAbs	Negative	Positive	Positive
TgAbs	Positive	ND	ND
TSHRabs	Negative	Negative	Negative
Ultrasonography	Homogeneous goiter	Homogeneous goiter	Homogeneous goiter
Scintiscan	No uptake ^{99}Tc	No uptake ^{123}I	No uptake ^{123}I
Second phase of thyroiditis: hypothyroidism			
TSH (N: 0.27–4.2 mIU/l)	53	50	4.3
FT4 (N: 9.3–17 ng/l)	1.9	2.48	7
FT3 (N: 2.57–4.43 ng/l)	1.28	ND	ND
Months to hypothyroidism	5	6	2
IFN- α continued	Yes	Yes	No (stopped during thyrotoxicosis phase)

ND, not done.

Figure 1 Thyroid scintiscan at the first and second thyrotoxic episodes. (a and b) Case 1, (c and d) case 2 and (e and f) case 3.

patient was asymptomatic, no treatment was prescribed and 1 month later the respective values of TSH and FT4 were nearly normal: 6.3 mIU/l and 6.6 ng/l. This patient's clinical picture was typical of silent thyroiditis

with spontaneous improvement of hypothyroidism. Then, in late May, hyperthyroidism recurred with TSH <0.02 mIU/l, FT4 29.4 ng/l and FT3 13 ng/l (Table 2) and with TSHRabs (human TRAK assay) >40 IU/l

Table 2 Recurrence of hyperthyroidism in three cases.

Parameter	Case 1	Case 2	Case 3
Months to recurrence	9	8	11
TSH (N: 0.27–4.2 mIU/l)	<0.02	<0.02	<0.02
FT4 (N: 9.3–17 ng/l)	39	29.4	9
FT3 (N: 2.57–4.43 ng/l)	18	13	ND
TPOAbs (N <130 IU/ml)	470	ND	ND
TgAbs (N <130 IU/ml)	462	ND	ND
TSHRabs	Positive	Positive	Positive
Ultrasonography	Vascularized goiter	Goiter	Goiter
Scintiscan	Intense ^{99}Tc uptake	Intense ^{123}I uptake	Intense ^{123}I uptake
Treatment of thyrotoxicosis	ATD and LT4	ATD and LT4	ATD
IFN- α continued	Yes	No	No

ATD, anti-thyroid drug.

(N: <2) and intense homogeneous ^{123}I uptake by the thyroid (52%) (Fig. 1d). These findings were highly suggestive of Graves' disease. Carbimazole and LT4 were prescribed and IFN- α was discontinued.

Evolution was unremarkable under the treatment. The hormonal evolution of the patient is shown in Fig. 2.

Case 3

A 47-year-old man with hepatitis C started treatment with pegylated IFN- α and ribavarin in September 2003. He had no known personal or familial history of thyroid disease. His initial TSH level was normal (1.36 mIU/l). Six months later (March 2004), his TSH level fell to 0.01 mIU/l, with FT4 at 12.9 ng/l (N: 9.3–17 ng/l) and FT3 at 4.6 ng/l (N: 2.5–4.4 ng/l) (Table 1). The investigative work-up showed a painless homogeneous goiter found during the physical examination, normal urinary iodine at 64 $\mu\text{g}/24\text{ h}$, TPOAbs

111 IU/ml (N: <60 IU/ml), negative TSHRabs (human TRAK assay) and negligible ^{123}I uptake on thyroid scintiscan (1.5%) at 5 h (Fig. 1e).

IFN- α was discontinued. Two months later (May 2004), subclinical hypothyroidism appeared, with TSH at 4.3 mIU/l and FT4 at 7 ng/l. In September 2004, hyperthyroidism recurred with TSH <0.02 and FT4 19 ng/l (Table 2), with TSHRabs becoming positive (human TRAK assay) at >3 IU/l (N: <2) and homogeneously intense scintigraphic I uptake (Fig. 1f), a picture corresponding to Graves' disease. Carbimazole was prescribed with an unremarkable evolution.

Discussion

Thyrotoxicosis developing during IFN- α treatment may be due to silent destructive thyroiditis or Graves' hyperthyroidism. Both possibilities have been described (1). In addition to hyperthyroidism, diagnosis of Graves'

Figure 2 Case 2: evolution of FT4 (right-hand scale) and TSH (left-hand scale) during treatment with IFN- α .

disease relies on TSHRAb determination and thyroid scintigraphy (6). Biphasic thyroiditis usually requires no specific treatment, as thyrotoxicosis resolves spontaneously, either followed or not followed by hypothyroidism. In contrast, Graves' disease usually has to be treated with prolonged anti-thyroid drug administration, surgery or ^{131}I .

Our patients' histories are unusual, as their thyroid disease progressed from 'classical' silent thyroiditis, albeit exceptionally severe for patient 1, to Graves' disease, the diagnosis of which was confirmed by the usual criteria. Such cases illustrate the importance of precise differential diagnosis of thyrotoxicosis in patients treated with IFN. In patient 1, for instance, carbimazole was unnecessarily prescribed during the first thyrotoxicosis episode, and recurrence was first taken for a new episode of destructive thyroiditis and treated with corticotherapy, as suggested by some authors (1) before Graves' hyperthyroidism was recognized.

Several other case reports (7–9) describe the evolution from thyroiditis to Graves' disease in patients treated with IFN- α . However, these case reports generally described incomplete forms of thyroiditis and/or Graves' disease, and lack comprehensive work-ups. In 1993, Eugène *et al.* (7) described a woman who, after 4 months on IFN- α , successively developed symptomatic hypothyroidism then Graves' disease. In 1995, Koizumi *et al.* (8) reported on a woman who, after 3 months on IFN- α , successively developed transitory thyrotoxicosis, followed 3 months later by recurrent hyperthyroidism with the appearance of high titer TSHRabs. Braga-Brasaria & Basaria (9) described the following sequence of events that occurred in a 51-year-old woman: asymptomatic thyrotoxicosis early during IFN- α therapy, then clear-cut hypothyroidism, followed several months later by hyperthyroidism corresponding to Graves' disease (9).

In this study we have described, in three patients, the previously undescribed 'triphasic' evolution of autoimmune thyroid disease with immunological and scintigraphic changes characteristic of the two successive diagnosis. Because a specific immunological work-up was obtained during each of the phases of thyrotoxicosis, we were able to exclude the possibility of modified TSHRab function – from stimulating to blocking and back to stimulating – as Chen *et al.* (10) described in four patients.

The clinical presentation in our three patients share some common points. They were three men without any recognized personal or familial history of anti-thyroid autoimmunity (although anti-TPOAb was not checked at the beginning of IFN treatment as it is a well-known thyroid autoimmunity risk factor (11). The time to the appearance of the destructive hyperthyroidism phase was 4–6 months, with the Graves' disease phase arising at 8–11 months. These intervals were also reported for similar cases (7–9).

In none of the cases was Graves' disease associated with orbitopathy. The attitude towards continuation of IFN- α therapy during thyrotoxic phases was not the same in our three patients. In patient 1, IFN- α therapy was continued despite severe thyrotoxicosis, a therapeutic choice that is still debated (1–3, 6, 10–12). This patient's favorable hepatitis C viremia evolution, at crucial times during his thyroid disease, led us to choose this pragmatic approach. The progression of his Graves' disease, which responded well to carbimazole, did not differ from that of our other two patients in whom treatment had been stopped during the first or second thyrotoxic phase.

This particular complication of IFN- α administration is certainly more common than suggested by the several case reports published, and merits further investigation with prospective monitoring of patients treated and precise etiological work-ups of the hyperthyroidisms occurring under IFN- α .

In these three patients treated with IFN- α , silent thyroiditis led to full-blown Graves' disease. We can only speculate about the mechanism of action of IFN- α in this process and this is of interest as IFN-mediated thyroid disease could constitute a model for human autoimmunity (13). With regard to the destructive phase of the disease, evidence has accumulated in favor of an autoimmune process, as it was demonstrated that production of thyroid autoantibodies preceded thyroid dysfunction (14) and, indeed, this phase looks like postpartum thyroiditis (15) and silent thyroiditis. Moreover, Graves' disease occurring after biphasic thyroiditis does not seem to be specific to IFN- α , as several case reports have described it after subacute thyroiditis (16), postpartum thyroiditis (17, 18) or spontaneous thyroiditis (16) or even after treatment of euthyroid goiter by ^{131}I (19). Progression towards Graves' disease is even more frequent for patients with a personal history of Graves' disease (16). The TSHRab production in susceptible individuals could thus be induced by the destruction of thyroid follicles that occurs during the course of thyroiditis, regardless of their cause. In animal models, immunization with TSH receptor cDNA is able to induce production of TSHRabs and even hyperthyroidism in some cases (20). Treatment with IFN- α might be a major sensitizing factor in this autoimmunization-like spontaneous immunostimulation of the postpartum period or immune restoration in successfully treated HIV-infected patients (21), situations which have recently been associated with the occurrence of Graves' disease.

In conclusion, IFN- α is able to induce all kinds of thyroid autoimmune disease. The biphasic forms of thyrotoxicosis due to silent thyroiditis are a particularly frequent side-effect of this drug. Indeed, treatment with this molecule has led us to report this new clinical form of thyrotoxicosis that fluctuates between silent thyroiditis and Graves' disease. An

appropriate name might be IFN- α -induced 'triphasic' thyrotoxicosis.

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