

## Graves' Hyperthyroidism Showing Transient Hypothyroidism during Interferon Therapy for Chronic Hepatitis Type C

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**Abstract.** We report a patient with Graves' disease in whom thyroid function was changed from initial hyperthyroidism to transient hypothyroidism and back to hyperthyroidism during interferon (IFN) therapy. A 43-year-old man was admitted to our hospital to receive IFN treatment for chronic active hepatitis (type C) in June 1998. His thyroid function was normal and testing for thyroid gland antibodies (TSH binding inhibitor immunoglobulins; TBII, anti-thyroglobulin antibodies; TgAb and anti-thyroid peroxidase antibodies; TPOAb) was negative before IFN therapy. The patient had neither history of thyroid disease nor any particular family history. He developed hyperthyroidism four months after its initiation of IFN therapy. When he was hyperthyroid, TBII, the activity of thyroid-stimulating antibodies (TSAb) and thyroid stimulation-blocking antibodies (TSBAbs) were 40.2% (normal range,  $-15 \sim +15.0\%$ ), 1201% (normal range,  $\leq 180\%$ ) and 52.0% (normal range,  $\leq 45.6\%$ ), respectively. Thyroid  $^{99m}\text{Tc}$ (technetium)-uptake ratio (Tc-UTR) was 1.07% (normal range, 0.5–3.0%). He transiently developed hypothyroidism in December 1998 and recurrent hyperthyroidism in February 1999. When he was hypothyroid, TBII, TSAb and TSBAbs were 74.3%, 769% and 95.9%, respectively. To investigate the mechanism of his fluctuating thyroid status, we serially assessed the serum levels of cytokines (TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-2, IL-4) and the soluble form of ICAM-1 (sICAM-1) as well as the activities of two types of TSH receptor antibodies (TRAb), TSAb and TSBAbs, before and after IFN therapy. There were no characteristic changes of cytokines or sICAM-1 during the follow-up period. The transient hypothyroid state may be explained by two possible mechanisms: one may be due to the shift in the balance between the stimulating and blocking types of TRAb, and the other may be due to the complication of destructive thyroiditis that developed during IFN therapy.

**Key words:** Graves' disease, Interferon, Chronic hepatitis

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**INTERFERON** (IFN) therapy has been established as the treatment of choice for chronic viral hepatitis. However, the induction of autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and the development of thyroid dysfunction, has also been reported during IFN treatment. Among these

diseases, thyroid autoimmunity appears to be the most frequent [1]. We previously reported a case of Graves' hyperthyroidism during IFN therapy [2]. Here we report another case of Graves' disease in whom thyroid function changed from initial hyperthyroidism to transient hypothyroidism and back to hyperthyroidism during IFN therapy.

It is now widely accepted that there are at least two types of TSH receptor antibodies (TRAb) present in the sera of patients with autoimmune thyroid diseases. One is a stimulating type known to be responsible for the development of hyperthyroidism due to Graves'

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disease, while the other is a blocking type, which inhibits TSH stimulation of the thyroid, thereby inactivating the thyroid and causing primary hypothyroidism. On the other hand, a correlation between the serum concentrations of the soluble form of intracellular adhesion molecule-1 (sICAM-1), believed to be a potential source of circulating leukocytes, and immunologic disease activity has been recently reported in autoimmune vascular and endocrine diseases [3, 4]. The ICAM-1 expression on the cell surface of circulating leukocytes is activated by proinflammatory cytokines such as tumor necrotic factor- $\alpha$  and interleukin, resulting in the elevation of serum concentration of sICAM-1 [5, 6]. In this paper, to investigate the mechanism of fluctuating thyroid function, we serially evaluated the role of certain cytokines (TNF $\alpha$ , IFN $\gamma$ , IL-1 $\beta$ , IL-2, IL-4) and the soluble form of ICAM-1 in addition to activities of two types of TRAb before and after IFN therapy, which were assessed at both hyperthyroid and hypothyroid states.

## Materials and Methods

Serum concentration of free T3, free T4 and TSH were determined with a chemiluminescent enzyme immunoassay using commercially available kits (Chemilumi ACS-TSH II, ChemilumiACS-FT3 II, ChemilumiACS-FT4 II, Roche Diagnostics, Indianapolis, IN, USA). The normal ranges of serum FT3, FT4 and TSH levels were set at 2.13–4.07 pg/ml, 0.95–1.74 ng/dl and 0.38–3.64  $\mu$ U/ml, respectively. TBII activity was measured with a radioreceptor assay using a commercially available kit (TRAb-Cosmic II, Cosmic Corporation, Tokyo, Japan). The normal range of serum TBII levels was set at  $-15 \sim +15\%$ . Serum levels of TgAb and TPOAb were determined by RIA (TgAb-Cosmic and TPOAb-Cosmic, Cosmic Corporation, Tokyo, Japan) (normal range:  $\leq 0.3$  U/ml for both assays).

TSAb and TSBAb were measured using Kasagi's method with a commercially available bioassay RIA kit (TSAb kit Yamasa, Yamasa Corp., Chiba, Japan) [7]. TSAb activities were expressed as a percentage of cAMP production generated in porcine thyroid cells that contained test pooled immunoglobulin (Ig) (normal range,  $<180\%$ ). TSBAb activities were calculated and expressed as follows:  $(1 - (c - d)/(a - b)) \times 100\%$ , where *a* is cAMP generated in the presence of Ig from normal pool serum and bovine TSH (100  $\mu$ U/ml); *b* is

cAMP generated in the presence of Ig from normal pooled serum; *c* is cAMP generated in the presence of test Ig and bovine TSH (100  $\mu$ U/ml); and *d* is cAMP generated in the presence of test Ig (normal range,  $\leq 45.6\%$ ) [8]. The serum concentrations of TNF- $\alpha$  were determined by enzyme-linked immunosorbent assay (ELISA) (Japan Immunoresearch Laboratories Co. Ltd., Tokyo, Japan). Intra- and inter-assay variances of TNF- $\alpha$  were 1.6–7.8% and 1.8–6.2%, respectively. The serum concentrations of IL-1 $\beta$  and IL-2 were determined by ELISA (BioSource International, Camarillo, CA, USA). Intra- and inter-assay variances of these cytokines respectively were 4.1–4.7% and 6.0–7.3% for IL-1 $\beta$ , and 5.5–7.8% and 7.7–8.6% for IL-2. The serum concentration of IFN- $\gamma$  was determined by ELISA (BioSource Europe, Nivelles, Belgium). Intra- and inter-assay variances of IFN- $\gamma$  were 3.6–5.7% and 6.3–7.5%, respectively. The serum concentration of IL-4 was assayed as described in a previous report [9]. sICAM-1 was measured by ELISA (R&D Systems, Minneapolis, MN, USA). Intra- and inter-assay variances of sICAM-1 were 3.3–4.8% and 6.0–10.1%, respectively. Serum samples were taken serially and kept frozen at  $-20^\circ\text{C}$  until the subsequent assays for TSAb and TSBAb were performed.  $^{99\text{m}}\text{Tc}$  thyroid uptake was measured 20 min after an iv injection of 2 mCi of [ $^{99\text{m}}\text{Tc}$ ]-pertechnetate (normal range: 0.5–3.0%).

## Case Report

The subject of our study was a 43-year-old Japanese man who was diagnosed as having chronic hepatitis type C in January 1998. He had a history of gastrectomy for a duodenal ulcer and had received a blood transfusion in 1974. He had neither history of thyroid disease nor any particular family history. A liver biopsy revealed chronic active hepatitis. The patient was admitted to our hospital to receive IFN therapy in June 1998. Table 1 shows the laboratory data on admission. The values of transaminases were normal. The level of hepatitis C virus (HCV) RNA was  $3.02 \times 10^5$  copies per ml of peripheral blood and the genotype of the HCV was type II. The results of the patient's thyroid function tests before IFN therapy were as follows (Table 2): FT4, FT3 and TSH were 1.40 ng/dl, 4.0 pg/ml and 1.98  $\mu$ U/ml, respectively; TBII was negative (5.7%). In addition, his thyroid autoantibodies to both

**Table 1.** Laboratory data before the start of IFN therapy

Hematological examination				Immunoserology	
RBC	425 × 10 <sup>4</sup> /mm <sup>3</sup>	WBC	7300 /mm <sup>3</sup>	anti-HBs	(-)
Hgb	13.1 g/dl	Neutro	54.4%	anti-HCV	(+)
Hct	39.3%	Eos	2.2%	HCV-RNA	3.02 × 10 <sup>5</sup> copies/ml
		Baso	0.4%	TBII	5.7%
PBC	28.4 × 10 <sup>4</sup> /mm <sup>3</sup>	Lymp	31.8%	TgAb	<0.3 U/ml
		Mono	9.2%	TPOAb	<0.3 U/ml
		Luc	1.9%		
Urinalysis Pro (-) Sug (-) occult blood (-)				Thyroid function	
				TSH	1.98 μU/ml
				FT3	4.0 pg/ml
				FT4	1.40 ng/dl
Blood chemistry					
GOT	33 IU/l	U-A	4.1 mg/dl	Na	137 mEq/l
GPT	36 IU/l	T-CHO	168 mg/dl	K	3.9 mEq/l
LDH	336 IU/l	T-G	53 mg/dl	Cl	101 mEq/l
ALP	209 IU/l	HDL-C	45 mg/dl	Ca	9.0 mg/dl
T-Bil	0.7 mg/dl	T-P	6.9 g/dl	Glu	74 mg/dl
BUN	12.3 mg/dl	Alb	3.9 g/dl	Amy	70 mg/dl
Cr	1.0 mg/dl				

TBII: TSH binding inhibitory immunoglobulin, TgAb: thyroglobulin antibody, TPOAb: thyroid peroxidase antibody.

**Table 2.** Clinical course and changes in representative findings

Date	TSH (μU/ml)	FT3 (pg/ml)	FT4 (ng/dl)	TBII (%)	TSAb (%)	TSBAb (%)	cAMP(a) (pmol/ml)	cAMP(b) (pmol/ml)	cAMP(c) (pmol/ml)	cAMP(d) (pmol/ml)	TPOAb (U/ml)	TgAb (U/ml)	99mTc- UTR(%)
Jun. 12, 1998	1.98	4.0	1.40	5.7							<0.3	<0.3	
Jul. 10, 1998					92.8	36.8	18.4	1.3	12.0	1.2			
Jul. 24, 1998	2.00	3.1	1.27	2.9							<0.3	<0.3	
Sep. 4, 1998	<0.03	6.0	2.86	10.1	365						<0.3	0.5	
Oct. 2, 1998	<0.03	8.4	3.31	40.2	1201	52.0					3.5	1.6	
Oct. 22, 1998													1.07
Oct. 30, 1998					992	81.3	18.4	1.3	16.1	12.9			
Nov. 13, 1998	15.12	2.2	0.79	74.3	769	95.9	18.4	1.3	10.7	10	3.8	4.4	
Dec. 14, 1998	47.70	2.2	0.78	73.1	783	71.7					5.6	6.0	
Jan. 11, 1999	18.33	3.0	1.04	49.2	662	78.4	18.4	1.3	12.3	8.6			
Feb. 8, 1999	<0.03	5.3	1.86	49.2	779	64.9					4.0	4.4	
Mar. 8, 1999	<0.03	8.5	3.03	36.8	665	0.3					3.4	2.9	

TSAb: thyroid-stimulating antibody, TSBAb: thyroid stimulation-blocking antibody, cAMP(a) is cAMP generated in the presence of Ig from normal pool serum and bovineTSH (100 μU/ml), cAMP(b) is cAMP generated in the presence of Ig from normal pool serum, cAMP(c) is cAMP generated in the presence of test Ig and bovineTSH (100 μU/ml), and cAMP(d) is cAMP generated in the presence of test Ig.

thyroid peroxidase and thyroglobulin were negative. The patient was treated with natural IFNβ (Interferon Beta Mochida, Mochida Pharmaceutical, Japan) at a daily dose of 6 million units (MU) for the first 4 weeks, followed by recombinant IFNα-2a (Roferon-A, Nippon Roche, Japan) at a dose of 9 MU thrice weekly for the next 20 weeks from June to December 1998.

Four months after the initiation of IFN therapy (in October 1998), he complained of palpitation, excessive sweating, and heat intolerance. Laboratory data revealed thyrotoxicosis (FT4 3.31 ng/dl, FT3 8.4 pg/ml, TSH <0.03 μU/ml) with positive TBII (40.2%). Thyroid ultrasonography showed a homogeneous and isoechoic pattern in a slightly enlarged thyroid gland.

TSAb and TSBAb activities were 1201% and 52.0%, respectively. Based on these laboratory findings, this patient was diagnosed as having Graves' hyperthyroidism. The  $^{99m}\text{Tc}$  thyroid uptake 20 days after the initial diagnosis of hyperthyroidism was 1.07%. The patient was treated with propranolol (30 mg per day) from October 1988.

Since his complaints, such as palpitation, excessive sweating, and heat intolerance, disappeared within one month after commencing propranolol, the patient was followed without any antithyroid drug treatment. He spontaneously developed a hypothyroid state in December 1998. His thyroid test revealed the elevation of TSH level (47.7  $\mu\text{U/ml}$ ) and decreased concentrations of FT3 (2.2 pg/ml) and FT4 (0.78 ng/dl). When he showed hypothyroidism, the activities of both TSAb and TSBAb were 769% and 95.9%, respectively. In addition, cAMP production from porcine thyroid cells in the presence of test Ig and bovine TSH was much lower than that in the presence of Ig from normal pooled serum and bovine TSH. The patient thereafter developed recurrent hyperthyroidism in February 1999. Thyroid function tests showed undetectable TSH (<0.03  $\mu\text{U/ml}$ ) and elevated FT3 (5.3 pg/ml) and FT4 (1.86 ng/dl) levels. Several serum cytokines and sICAM-1 levels measured serially during the treatment (before IFN treatment, the initial hyperthyroid state, and the hypothyroid state during IFN treatment) revealed no characteristic changes (Table 3). When the patient developed recurrent hyperthyroidism, both TBII and TSAb activities remained positive. He was treated with methimazole (15 mg per day) from March 15, 1999 to June 14, 1999. The dose of methimazole was

then reduced to 10 mg per day. After that, he was euthyroid with a normal TSH level on January 17, 2000, when he was treated with a lesser dose (5 mg per day) of methimazole. The treatment was finally stopped on September 13, 2002. Our present case required anti-thyroid drug treatment to achieve the remission of Graves' hyperthyroidism for more than three years. Now he has been under follow-up without any antithyroid drug treatment.

## Discussion

Various types of thyroid dysfunction have been reported in certain patients during IFN therapy for viral hepatitis [10–12]. Among these, hypothyroidism (62%) seems to be the most frequent, followed by silent thyroiditis (16%) and Graves' disease (11%) [13].

The mechanism by which IFN induces thyroid dysfunction remains incompletely understood, but the autoimmune mechanism is thought to play an important role. IFN- $\alpha$  enhances the surface expression of major histocompatibility complex (MHC) class I antigens [14], which are known to activate cytotoxic T cell function. IFN- $\alpha$  also induces MHC class II antigens on thyroid cells in patients with autoimmune thyroid diseases [15, 16]. The aberrant expression of MHC antigens on the cell surface, in association with that of cellular antigens, may be sufficient to interrupt tolerance and induce autoantibody production [17]. Cytokines such as TNF- $\alpha$  and IL- $\beta$ , that are induced by IFN- $\alpha$  [18], may directly or indirectly affect the thyroid function due to their immunomodulatory effects.

The thyroid function of our present case changed from initial hyperthyroidism to transient hypothyroidism and back to hyperthyroidism during IFN therapy. We speculated that the changes in the serum levels of various cytokines such as TNF- $\alpha$  and IL- $\beta$ , which were shown to be affected by IFN- $\alpha$  in an *in vitro* study [18], were related to the course of the fluctuating phases of hypo- and hyperthyroidism. Therefore, we carried out the serial measurement of several serum cytokine levels, but could not detect any specific changes during the observation period. Although we examined the sICAM-1 concentrations, measurement of which has been shown to be useful to predict the response to IFN treatment [19] and to assess immunologic activities in untreated Graves' disease [20], they showed no significant changes during IFN therapy.

**Table 3.** Changes in the concentration of cytokines and ICAM-1

	before IFN treatment	initial hyperthyroid state during IFN treatment	hypothyroid state during IFN treatment
<cytokines>			
TNF $\alpha$ (pg/ml)	<5.0	<5.0	<5.0
IFN $\gamma$ (IU/ml)	0.3	0.2	<0.1
IL-1 $\beta$ (pg/ml)	<10	12	<10
IL-2 (pg/ml)	<0.8	<0.8	<0.8
IL-4 (pg/ml)	<2.0	<2.0	<2.0
sICAM-1 (ng/ml)	611	482	636

TNF $\alpha$ : tumor necrosis alpha, IFN- $\gamma$ : interferon-gamma, IL-1 $\beta$ : interleukin-1 beta, IL-2: interleukin-2, IL-4: interleukin-4, sICAM-1: soluble form of intracellular adhesion molecule-1.

The changes in the levels of activity of the two types of TRAb, TSAb and TSBAb, play an important role in the clinical course of autoimmune thyroid diseases [21, 22]. In fact, when increased TSBAb was observed during IFN therapy, some cases showed transient hypothyroidism [23, 24]. This prompted us to investigate whether the changes in the levels of activity of the two types of TRAb can possibly explain the fluctuating thyroid levels in our case. A high level of TSAb activities, which was reported to be unaffected by serum TSH levels [8], was seen in this patient during both hyperthyroid and hypothyroid states. In contrast, TSBAb activities reached their maximum level when the patient developed transient hypothyroidism. Thus, one possible mechanism by which this patient showed transient hypothyroidism during IFN treatment may have been the changes in the levels of activity of the two types of TRAb, TSAb and TSBAb. However, we could not directly prove the presence of TSBAb because of sampling with high TSAb activities [8, 25].

Several studies have reported destructive thyroiditis following IFN treatment for chronic hepatitis [1, 11, 26]. Another possible mechanism by which this patient showed transient hypothyroidism during IFN treatment may have been the complication of destructive thyroiditis. The transient appearance of weak positive TRAb is sometimes noticed during destructive thyroiditis, and the development of Graves' hyperthyroidism following destructive thyroiditis is also occasionally observed. A positive level of TBII (40.2%) and increased activity of TSAb (1201%) in October 1988 may imply that he had

Graves' hyperthyroidism. However, the possibility that he had concomitant destructive thyroiditis, and that hyperthyroidism was followed by destruction-induced hypothyroidism cannot be completely ruled out.

In addition, thyroid dysfunction developed during IFN therapy in patients without pre-existing anti-thyroid autoantibodies is rare [27]. Our present case, however, showed no thyroid dysfunction or any anti-thyroid antibodies including TRAbs before IFN treatment. Although this patient had neither past nor family history of autoimmune disease, we cannot rule out the possibility that this patient had an underlying predisposition to autoimmune thyroid disease, because of insufficient data regarding HLA-antigen and single nucleotide polymorphisms of the cytotoxic T-lymphocyte antigen-4 (CTLA4) gene [28].

It is now apparent that IFN $\alpha$  treatment induces a variety of thyroid dysfunction. The clinical course of our present case of Graves' disease is unique in that the thyroid function was changed from initial hyperthyroidism to transient hypothyroidism and back to hyperthyroidism during IFN therapy. The approach which we took in this case, involving various examinations, such as measuring the activities of two types of TRAbs and serial serum levels of cytokines and sICAM-1, may assist in understanding the immunomodulatory effects of IFN therapy for chronic viral hepatitis. Further studies are required to elucidate the mechanism of immunomodulatory action caused by IFN treatment.

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