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THYROID DYSFUNCTION FOLLOWING ALPHA-INTERFERON TREATMENT FOR CHRONIC HEPATITIS C

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Abstract: In order to evaluate the influnces of IFNα on thyroid function, thyroid-stimulating hormone (TSH), total thyroxine (T4), free T4, tri-iodothyronine (T3), and thyroxine-binding globulin were examined in IFNα-treated 351 patients with chronic hepatitis C before and during therapy. As therapy, either 3 million units (MU) of human lymphoblastoid IFNα or 9MU of recombinant IFNα2a was administrated daily for the initial two weeks followed by three times a week for 22 weeks. There were nine patients showing thyroid dysfunction during IFNα therapy. They consist of one relapse of Graves' disease, one relapse of Hashimoto thyroiditis, one development of apparent thyroid insufficiency from subclinical hypothyroidism, five cases with transient hyperthyroidism and one case with transient hypothyroidism. T4 and T3 levels in most patients who transiently developed thyroid dysfunction were normalized spontaneously after the discontinuation of IFNα. Thyroid-related autoantibodies were positive in 4 patients before IFNα therapy and newly developed in one patient during therapy. Attention should be paid first to the previous histories of autoimmune thyroid diseases and the existence of thyroid-related autoantibodies for the prediction of development of thyroid dysfunction during IFNα therapy. In addition, serial examinations of TSH, T3 and T4 should be also necessary for early detection of transient thyroid dysfunction during IFNα therapy.

Index Terms

chronic hepatitis C, interferon therapy, thyroid function autoimmune disease.

INTRODUCTION

Interferon-alpha (IFNα) is known to lead to improvement in serum aminotransferase and liver histology in many patients with chronic hepatitis C[1-3]. However, IFN treatment is often accompanied with various adverse reactions. Besides common side effects, such as fever, chills, myalgia, arthralgia, fatigue, mild reversible bone marrow suppression, nausea and diarrhea, there are also reported exacerbations or developments of autoimmune diseases[4-15]. It is natural for IFNα treatment to lead to such involvement with autoimmune diseases because

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IFNα is a potent immunomodulatory agent and known to enhance the expression of major histocompatibility gene complex (MHC) class I antigen on several cell types. Among the autoimmune diseases induced by IFNα administration, thyroid disorders are most often documented[4,5,10,13-15].

In reviewing our own experience of treating 351 patients with chronic hepatitis C by IFNα, there were 9 patients who developed thyroid dysfunction. In this report, we describe these 9 patients and clinically analyze the factors underlying for the development of thyroid dysfunction.

MATERIALS AND METHODS

Since April 1991, 351 patients with chronic hepatitis C were treated with IFNα. As shown in Table 1, they include 236 males and 115 females whose ages ranged from 18y.o. to 69y.o. (mean 51.5y.o.). Liver biopsies were performed in all patients before IFNα therapy. As IFNα, either human lymphoblastoid IFNα (natural IFNα, nIFNα, Sumiferon^{R}) or recombinant IFNα2a (rIFNα, Canferon^{R}) was used at doses of 3 million units (MU) or 9MU, respectively. IFNα was usually given daily for the intial two weeks, followed by three times a week for 22 weeks. Thyroid-stimulating hormone (TSH), total thyroxine (T4), free T4 (fT4), tri-iodothyronine (T3), and thyroxine-binding globulin (TBG) were examined before and during IFNα therapy in order to evaluate the effects of IFNα on thyroid function. In most patients, blood samples were also tested serially for antithyroglobulin antibody (ATG) and antimicrosomal antibody (AMS) by hemoagglutination.

RESULTS

As shown in Table 2, the nine patients (six males and three females; aged from 38y.o. to 71y.o., mean 51.0y.o.) developed thyroid dysfunction during IFNα treatment. Five had been treated with rIFNα, four with nIFNα. Three patients developed hypothroidism and six patients hyperthyroidism. The results of thyroid function tests in these nine patients are summarized in Table 3. A brief clinical course is given below on each patient.

Case 1 56y.o. Female

She had been treated with thyroxine since March, 1991 for 12 months. In that period, the

Table 1. Characteristics of patients

Variable	Values
Patient number	351
Men and women	236, 115
Median age at start of therapy (yo)	51.5
Histology of liver	
CAH2A	222
CAH2B	68
CPH	61
Treatment	
Natural interferon-α	204
Recombinant interferon-α	147

Table 2. Clinical features of nine patients who developed thyroid dysfunction during therapy with interferon

Patient no.	Age (yo)	Liver histology	IFNα used	Sex	Thyroid abnormality	Onset
1	56	CAH2A	nIFNα	F	Hypo	8w
2	44	CAH2B	rIFNα	F	Hyper	16w
3	48	CAH2A	rIFNα	M	Hyper	8w
4	43	CAH2A	nIFNα	M	Hyper	24w
5	63	CAH2A	nIFNα	M	Hypo	24w
6	71	CAH2A	rIFNα	M	Hyper	6w
7	38	CAH2A	rIFNα	F	Hyper	24w
8	49	CAH2A	nIFNα	M	Hyper	10w
9	47	CAH2A	rIFNα	M	Hypo	4w

Table 3. Results of thyroid function tests in nine patients who developed thyroid dysfunction while being treated with IFNα

Patients no.	before/during IFNα THerapy	TSH 0.3~3.5μu/ml	T3 0.8~1.8ng/ml	T4 4.6~12.6μg/dl	free—T4 0.85~2.15ng/ml	Thyroid test	Microsome test
1	before	0.45	1.6	8.5	1.21	102400	102400
	10w	150	0.6	1.1	0.24	25600	25600
2	before	1.7	1.3	7.5	0.6	(−)	100
	16w	0.08	2.4	16.6	1.5	(−)	1600
3	before	1.8	0.8	4.7		(−)	(−)
	12w	0.05	2.0	15.5		(−)	(−)
4	before	1.0	1.5	15.6		(−)	(−)
	24w	0.05	3.3	23.2		(−)	(−)
5	before	2.1	1.6	10.9		(−)	(−)
	24w	120	0.6	1.7		400	400
6	before	1.2	1.1	10.3		(−)	1600
	12w	0.05	2.3	15.8		(−)	400
7	before	1.7	1.4	12.4		(−)	(−)
	24w	0.05	3.4	23.7		(−)	(−)
8	before	1.7	1.1	11.6	1.26	(−)	(−)
	12w	0.06	1.8	14.9	2.7	(−)	(−)
9	befor	28.9	1.3	7.3		6400	25600
	4w	50.9	8.8	4.3	0.4	6400	25600

elevation of ALT level and the presence of anti-HCV in serum were found. Liver biopsy was performed on July 28, 1992 and the liver histology showed chronic active hepatitis (CAH) 2a according to the European classification. Natural IFNα was started on September 8. Although she remained in euthyroid and free from any thyroid-related symptom for 6 months without medication, she began to feel fatigue in the 8th week of therapy. Thyroid function tests on the 10th week were abnormal (TSH 150 microunits (μU)/ml, T3 0.6 ng/ml, T4 1.1 μg/dl). Thyroxine was then prescribed and the 24-week administration of IFNα was completed. Thyroid test (TT) and microsome test (MT) were already positive in high titers before IFN treatment and tended to decrease with the use of IFNα (Fig. 1).

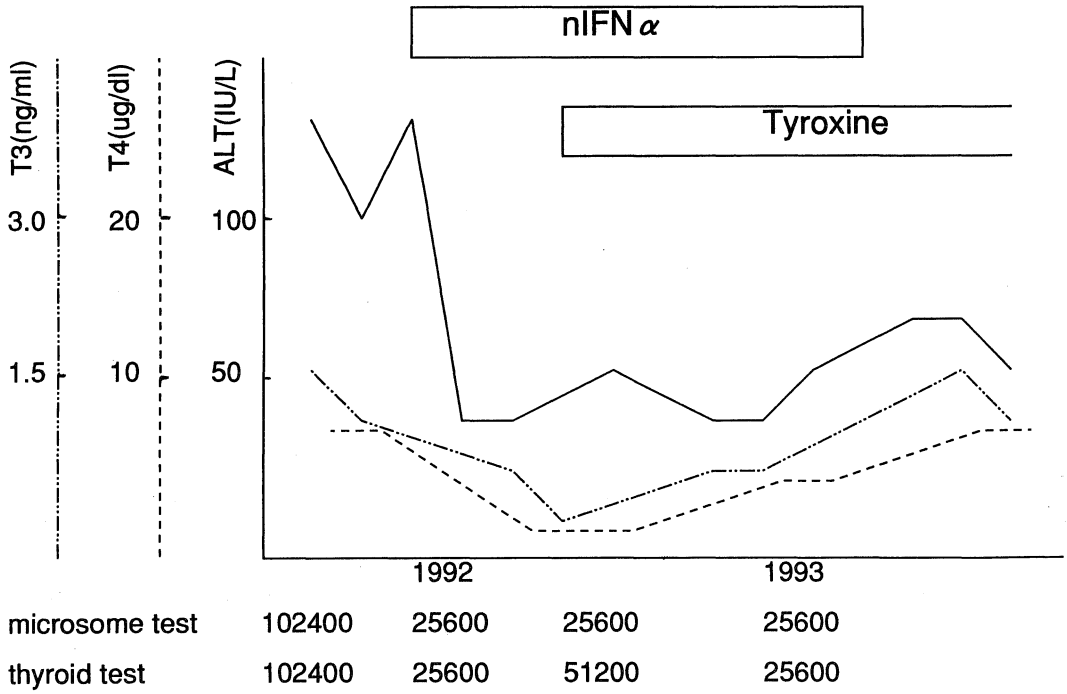

Fig. 1. Clinical course of Case 1.

Case 2 44y.o. Female

She came to us because of shortness of breath, tachycardia and fatigue in August, 1990. The diagnosis of Graves' disease was made. With the introduction of methyl-mercapto-imidazol (MMI), thyroid function returned to normal and remained in euthyroid even after the drug was stopped in June, 1991. She was also found to have chronic hepatitis C by blood examination at her first visit. Then rIFNα was started in September, 1992 for chronic hepatitis C. Before IFNα therapy, serum T3 and T4 levels were within normal ranges, but they began to increase and reached the hyperthyroid ranges in the 16th week of IFN therapy, when she also developed fatigue and tachycardia similar to the symptoms which appeared before at the diagnosis of Graves' disease. Thyroid function tests did not normalize during the remaining IFNα period. However, the symptoms disappeared with the prescription of a beta-blocker and a minor tranquilizer. Since serum T3 and T4 remained at elevated levels even after the finish of the 24-week IFNα therapy, MMI was started in July, 1993. Serum T3 and T4 reached normal values in two months. In this case, the titer of MT increased during IFNα therapy. In addition, the elevation of TSH-binding inhibitor immunoglobulin (TBII ; nornal, <15 %) was observed (Fig. 2).

Case 3 48y.o. Male

This patient with chronic hepatitis C had a history of transfusion in 1970, when the resection of the upper lobe of right lung was performed. There was no history of thyroid disorders. Recombinant IFNα was initiated in August, 1992. Serum T3 and T4 levels were normal before and the 4th week of IFN therapy. At the 8th week of therapy, he developed

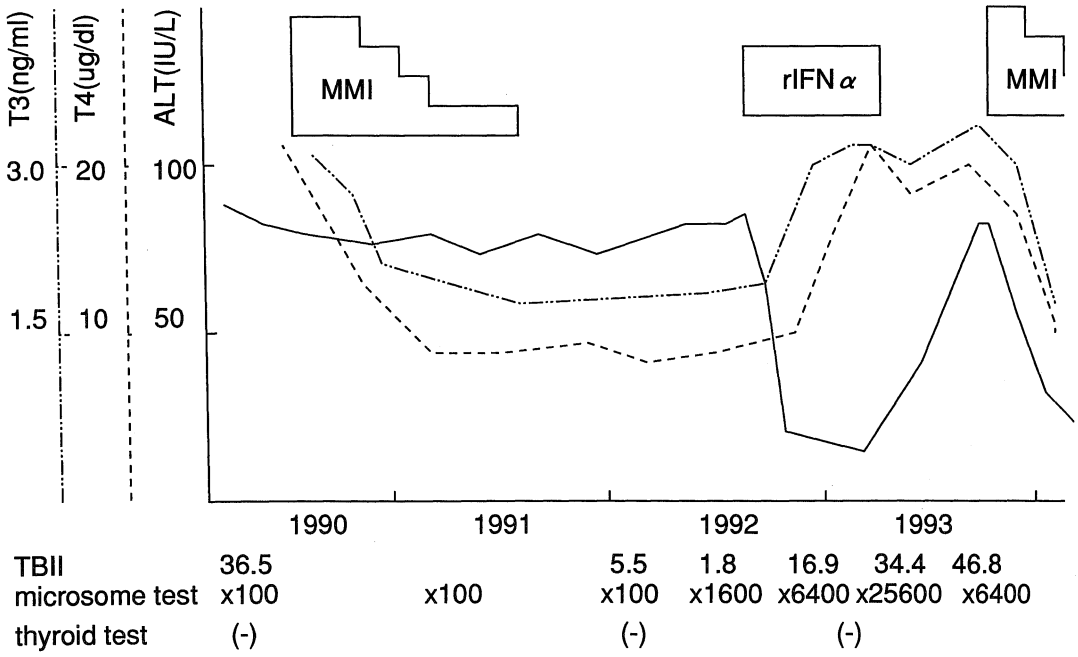

Fig. 2. Clinical course of Case 2.

finger tremors. Thyroid function tests at the 12th week of therapy disclosed the presence of hyperthyroidism. IFNα administration was discontinued and MMI was prescribed at a daily dose of 5 mg for the following 20 weeks. The levels of serum thyroid hormones returned to normal in 4 weeks. At the 9th week after the discontinuation of IFNα, his T4 was 1.0 μg/dl (normal 4.6-12.6). T3 0.6 ng/ml (normal 0.8-1.8) and TSH 7.0 μU/ml (normal 0.3-3.5). MMI was stopped at this point. Thyroid function returned to nomal in 4 weeks. Thyroid-related autoantibodies did not appear throughout the observation period.

Case 4 43y.o. Male

He had no history of thyroid diseases. Thyroid functions were normal at the 4th week and also at the 12th week of IFN therapy. He developed finger tremors and tachycardia in the last month of 24-week IFNα therapy. Thyroid function at the last week of therapy was in a hyperthyroid state; T4 23.2 μg/dl, T3 3.3 ng/ml, TSH $<$ 0.05 μU/ml. But these returned to normal without medication in 3 months. Thyroid-related autoantibodies did not develop.

Case 5 63y.o. Male

He had been in good health until 1985, when he had a gastorectomy because of gastric cancer. Transfusion at that time caused chronic hepatitis C following acute hepatitis. The 24-week administration of nIFNα was completed safely. T3, T4, TSH were in normal ranges at the 5th week of therapy. No symptom related to thyroid diseases was observed throughout the therapy period. However, blood examination of the last injection day of nIFNα disclosed elevation of TSH level (120 μU/ml) and decreasing T4 and T3 levels (1.7 μg/dl and 0.6 ng/ml, respectively). Both results of TT and MT turned to be positive. Although no treatment was

introduced for the correction of the hypothyroidism, serum T3 and T4 increased to normal levels in 3 months.

Case 6 71y.o. Male

He did not have previous history of thyroid diseases. Although he had positive result (x1600) of MT, thyroid function was normal before IFN therapy. T3 and T4 levels remained within normal ranges at the 4th week of therapy, but TSH level was less than 0.05 μU/ml. He complained of fatigue and palpitations after the 6th week of therapy. Thyroid function tests at the 12th week of therapy showed the presence of hyperthyroidism : T4 15.8 μg/dl, T3 2.3 ng/ml, TSH $<$ 0.05 μU/ml. The titer of MT was decreased to x400. IFNα was stopped at the end of the 12th week of therapy. Thyroid function spontaneously returned to euthyroid in 4 weeks after the discontinuation of IFNα.

Case 7 38y.o. Female

She had no history of autoimmune diseases. She underwent 24-week administration of rIFNα. Thyroid function of the 4th week of therapy was normal. She noted increasing fatigue and finger tremors at the 12th week of therapy. Blood examination at the 24th week showed hyperthyroidism; T4 23.5 μg/dl, T3 3.4 ng/ml and TSH $<$ 0.05 μU/ml. However, the hyperthyroidism improved after the finish of IFNα. Thyroid-related autoantibodies were not detected throughout the observation period.

Case 8 48y.o. Male

He had right nephrectomy in 1980 because of renal rupture caused by a traffic accident, but no history of thyroid diseases. He felt mild fatigue in the 10th week of IFNα treatment. Thyroid function at the 12th week of therapy showed a slight elevation of T4 level (14.9 μg/dl). MT and TT were negative at that point. The T4 values were 15.7, 13.8 and 12.8 μg/dl at the 16th, 20th and 24th week of IFNα therapy, respectively. Soon after the finish of IFNα treatment, T4 level became normal. Anti-thyroglobulin antibody and anti-microsomal antibody were detected at the end of IFNα therapy.

Case 9 47y.o. Male

Anti-thyroglobulin antibody and anti-microsomal antibody were present in serum at high titers before IFNα threrapy. T3 and T4 were in normal ranges but TSH level was elevated. With the use of rIFNα, T3 and T4 tended to decrease and TSH rose to more than 100 μU/ml. Therefore thyroxine was introduced at the 8th week of therapy. The 24-week IFNα therapy was then completed with thyroxine replacement therapy.

DISCUSSION

The development of thyroid dysfunction has been reported in patients receiving IFNα for long periods, and the incidence of thyroid dysfunction during IFNα therapy has been stated from 0%[14] to 50%[13]. In IFNα treatment for chronic hepatitis C, the development of thyroid dysfunction was observed in 2.5[4]-6%[15] of patients on IFNα therapy. In our study, 9 patients

out of 351 (2.6%) developed thyroid dysfunction. However it is possible that there were not included some patients who have developed just transient abnormal thyroid function without any symptom, since thyroid function was not examined so frequently.

The nine patients described in this report showed normal T3 and T4 levels at the start of IFNα treatment. However, two patients, Case 1 and Case 2, had histories of treatment for Graves' and Hashimoto's disease, respectively. Both these patients relapsed into their previous diseases by the use of IFNα. Therefore it was strongly suggested that IFNα therapy provoked underlying autoimmune thyroid diseases. Moreover, IFNα administration might make some pre-clinical autoimmune disease apparent. Indeed, in Case 9, the presence of hypothyroidism become overt by IFNα therapy. Then the existence of thyroid-related autoantibodies may also be an important clue for predicting the development of thyroid autoimmunity as well as the previous history. Actually, there were four patients who had thyroid-related autoantibodies before IFNα therapy. Therefore we should pay attention to the susceptibilities of autoimmune thyroid diseases which are manifested by the previous histories and the existence of thyroid-related autoantibodies.

It is noteworthy that there were 4 patients, Cases 4, 6, 7 and 8, who showed transient hyperthyroidism during IFNα therapy. Serum T3 and T4 levels were elevated for a limited period of IFNα treatment and became normal without antithyroid agents. In addition to these four cases, hyperthyroidism in Case 3 was easily corrected by a minimum dose of MMI and followed by transient hypothyroidism. In all of these 5 cases, an excess of thyroid hormone was developed during IFNα period and the discontinuation of IFNα normalized thyroid hormone levels. Two possibilities might be raised. IFNα may induce an excessive production of thyroid hormone by thyroid gland or just induce a leak of preformed hormone from the gland owing to some inflammatory injury. The measurement of radioactive iodine uptake could be useful for the differentiation. Recently Berris et al[15] reported a patient who showed transient hyperthyroidism with very low radioactive iodine uptake, subsequently followed by a hypothyroid state, suggesting destructive thyroiditis. Therefore it is reasonable to consider that IFNα initiate some mechanism, probably immune-mediated mechanism, jnjuring the thyroid gland. The hypothyroidism observed in Case 5 might be considered as a sequential event following a transient hyperthyroid state.

As postulated, inappropriate expression of major histocompatibility complex (MHC) class II antigen is a key event for the induction of immune-mediated cell injury, specially in thyroid autoimmune diseases[16]. In general, IFN-gamma is considered to play an crucial role as a potent inducer for MHC class II antigen expression[17,18], even though it was not identified what triggers IFN-gamma production as an initial event. While IFNα is not widely accepted to induce MHC class II antigen, however, it was recently reported that IFNα enhanced IFN-gamma production of peripheral blood mononuclear cells[19], suggesting a role of IFNα as a modulator of the cellular immune responses. Therefore the possibility should be taken into consideration that IFNα administration might induce and exacerbate autoimmune process. Actually, there are several clinical reports documenting the development of other autoimmune diseases such as systemic lupus erythematosus[8], rheumatoid arthritis[10] and hemolytic anemia[7]. We ourselves have also experienced the development of idiopathic thrombocytopenic purpura[12] and ulcerative colitis[11].

In conclusion, nine patients out of 351 developed thyroid dysfunction during IFNα therapy for chronic hepatitis C. There were observed relapses of preexisting autoimmune thyroid diseases in two patients, induction of clinically aparent thyroid insufficiency in one patient with subclinical hypothyroidism, and transient thyroid dysfunction in six patients. The transient thyroid dysfunction were considered to be due to destructive thyroiditis. These results support the idea that interferons may play an important role in the development or recurrence of autoimmune thyroid diseases. Threrefore it is necessary to examine thyroid function serially as well as thyroid-related autoantibodies for the early detection of autoimmne thyroid disorders during IFNα therapy for chronic hepatitis C.

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