CASE REPORT
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Interferon-Alpha Induced Severe Hypothyroidism Followed by Graves' Disease in a Patient Infected with Hepatitis C Virus

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Interferon-alpha (IFN-α) is an important therapeutic agent for hepatitis C virus (HCV) infection, but has various side effects including thyroiditis. We report a case of interferon-induced non-autoimmune hypothyroidism followed by autoimmune-medicated Graves' disease. A 59-year-old woman was diagnosed with chronic active hepatitis C; she had been treated with IFN-α and ribavirin for 24 weeks. Before starting the IFN-α, her thyroid function was normal and she was negative for autoantibodies. Severe hypothyroidism developed 5 weeks after halting the IFN-α, with the Graves' disease phase arising at 32 weeks. For accurate diagnosis and appropriate treatment of thyroid dysfunction during treatment with IFN-α, we need to understand and consider rare cases of multiphasic disorder involving both non-autoimmune and autoimmune thyroiditis induced by IFN-α.

Key Words: Interferons, Non-autoimmune hypothyroidism, Graves' disease

Introduction

Affecting more than 3.5 million individuals annually worldwide, hepatitis C virus (HCV) infection is among the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma.[1] Since 2001, pegylated-interferon-α (PEG-IFN-α) with ribavirin has been recommended as a standard therapy for chronic HCV. A type I interferon, IFN-α has many side effects, ranging from influenza-like symptoms to hematological effects, neuropsychiatric symptoms, and thyroid disease. Thyroid dysfunction has been reported in 2-13% of HCV-infected patients; however, this incidence increases to 15-40% with the use of interferon.[2]

Interferon-induced thyroiditis (IIT) was first reported in 1985, when the association between IFN-α and thyroid disease was recognized in patients treated with IFN-α for carcinoid tumors and breast cancer. IIT can be classified into autoimmune and non-autoimmune subtypes according to autoantibody status.[3] Autoimmune IIT can manifest as the development of thyroid antibodies without clinical disease, or as clinical disease including both autoimmune hypothyroidism (Hashimoto's thyroiditis) and autoimmune hyperthyroidism (Graves' disease). Non-autoimmune IIT can manifest as destructive thyroiditis or as hypothyroidism without thyroid antibodies.[2] Here, we report an unusual case of IFN-α-related thyroid dysfunction in a patient with HCV infection: severe hypothyroidism caused by non-autoimmune thyroiditis and subsequent autoimmune-mediated Graves' disease.

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Case Report

A 59-year-old Korean woman was diagnosed with chronic active hepatitis C based on a liver biopsy, and treated with pegylated IFN-α 80 μg weekly and ribavirin 800 mg daily for 24 weeks. Before treatment, her thyroid function tests were normal and all thyroid antibodies tested were negative, including anti-microsomal, anti-thyroglobulin, and anti-thyroid stimulating hormone (TSH) receptor antibodies. She had no personal or family history of thyroid dysfunction and the physical examination showed no manifestations suggesting thyroid disease, such as goiter or ophthalmopathy. After 12 weeks of treatment, her serum HCV RNA viral load became negative and remained so during follow-up. Her thyroid function tests were within the normal ranges 12 weeks after treatment and she had no symptoms during treatment. However, 5 weeks after completing treatment, she experienced mild fatigue and myalgia. Laboratory tests showed a decreased free T4 level, to 0.04 ng/dL (reference range, 0.79-1.86 ng/dL), with a TSH level over 100 μIU/mL (reference range, 0.14-4.05 μIU/mL) and negative thyroid antibodies. On thyroid ultrasonography, diffuse parenchymal heterogeneity was noted in the thyroid gland bilaterally, without increased vascularity. A diagnosis of severe hypothyroidism caused by non-autoimmune IIT was made and she was given levothyroxine 75 μg/day. After 7 weeks of treatment for hypothyroidism, the free T4 and total T3 levels increased slightly to 2.09 ng/dL and 229.9 ng/dL (reference range, 78-182 ng/dL), respectively, while the TSH level was suppressed mildly to 0.13 μIU/mL. Tc-99m scintigraphy showed slightly increased Tc uptake (Fig. 1A). The levothyroxine was tapered off over 18 weeks.

After 8 weeks, despite discontinuing the levothyroxine, she complained of lethargy and a 7 kg weight loss. Thyroid function tests showed thyrotoxicosis, elevated free T4 at 2.39 ng/dL, T3 at 224.9 ng/dL, and suppressed TSH 0.02 at μIU/mL. TSH receptor antibody was positive with an elevated titer of 5.4 IU/L (reference range, 0-1.5 IU/L). On Tc-99m scintigraphy, both thyroid lobes showed diffusely increased Tc uptake (Fig. 1B). Anti-microsomal and anti-thyroglobulin antibodies were negative. Ultimately, she was diagnosed with Graves' disease caused by the *de novo* production of TSH receptor antibody. Methima-

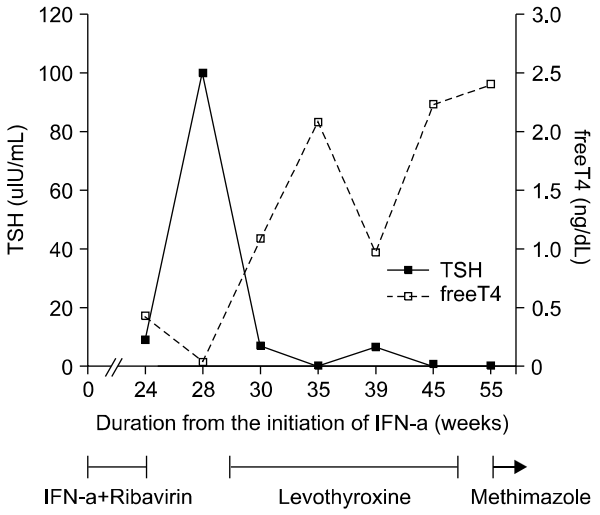

Fig. 2. The clinical course of thyroid function in the HCV-infected patient on IFN-α therapy: the biphasic pattern of thyroid function after initiation of IFN-α therapy.

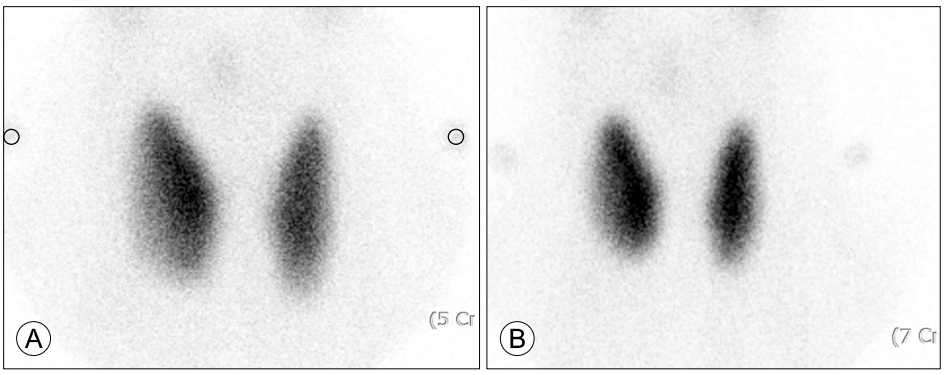

Fig. 1. Tc-99m scintigraphy in the thyrotoxic period. (A) After taking levothyroxine for hypothyroidism for 7 weeks. (B) Eight weeks after discontinuing levothyroxine with confirmed TSH receptor antibody positivity.

zole and beta-blockade were started and continued. Fig. 2 shows the biphasic course of the thyroid function tests of this patient.

This report describes two different features of IFN-α-induced thyroiditis in one patient with HCV infection: non-autoimmune hypothyroidism and subsequent autoimmune Graves' disease.

Discussion

Thyroiditis is among the most common side-effects of IFN-α therapy; subclinical thyroiditis occurs in 20-40% of patients and clinical thyroiditis in 5-10%.[4] IFN-α triggers thyroiditis in genetically predisposed individuals via both immune-modulatory and direct thyroid-toxic mechanisms.[4,5] Autoimmune IIT can manifest as clinical disease, i.e., Graves' disease or Hashimoto's thyroiditis, or as subclinical disease in which thyroid autoantibodies are present in the absence of abnormal thyroid functions. Non-autoimmune IIT, which comprises approximately 50% of IIT cases, can manifest as destructive thyroiditis or non-autoimmune hypothyroidism without detectable antibodies.[4-6]

Several studies have demonstrated that IFN induces thyroid cell death by necrosis *in vitro*, supporting the hypothesis that IFN can cause thyroiditis via a direct thyroid-toxic mechanism.[7,8] In our case, the patient's initial presentation after IFN therapy was compatible with non-autoimmune hypothyroidism, as the patient was hypothyroid without autoantibodies. Destructive thyroiditis, another manifestation of non-autoimmune IIT, usually starts with an early thyrotoxic phase and progresses to a hypothyroid phase, with complete resolution observed in most cases.[2] These are difficult to distinguish when a patient is in a hypothyroid state because both destructive thyroiditis and non-autoimmune hypothyroidism share a hypothyroid phase. Although we did not observe an early thyrotoxic phase in our patient, it is possible that the patient experienced very mild symptoms related to a thyrotoxic state that were overlooked. However, as destructive thyroiditis is usually followed by a mild or subclinical hypothyroid phase, our patient is more compatible with non-autoimmune hypothyroidism as she did not experience thyrotoxic symptoms and showed severe hypothyroidism.

In our case, the severe hypothyroid phase was followed by thyrotoxicosis with positive TSH receptor antibody, i.e., Graves' disease. Our patient began to exhibit mild thyrotoxicosis after 8 weeks of levothyroxine treatment for severe hypothyroidism. Although we confirmed TSH receptor antibody positivity several weeks after discontinuing levothyroxine, the mildly increased uptake on thyroid scintigraphy indicated that Graves' disease had already developed during the levothyroxine treatment. In addition to the typical single phasic pattern, such as hypothyroidism or hyperthyroidism, multi-phasic patterns have been reported, as in our case (summarized in Table 1). Kim et al.[9] described a woman with HCV infection who was treated with IFN-α and developed destructive thyroiditis followed by transient Graves' disease. Their patient was treated with IFN-α for 48 weeks and Graves' disease was diagnosed 2 months after completing treatment. As in our case, *de novo* production of thyroid antibody was observed. Tran et al.[3] also reported a case involving a tri-phasic pattern, with destructive thyroiditis followed by Graves' thyrotoxicosis. Bohbot et al.[10] reported three cases of IFN-α-induced tri-phasic thyroiditis. These patients initially experienced silent destructive thyroiditis, but eventually developed Graves' disease. Savvas et al.[11] reported IFN-α-induced Hashimoto's thyroiditis followed by Graves' disease.

As an underlying mechanism by which IFN can induce autoimmune thyroiditis, IFN-α activates several signaling pathways, including the Janus kinase/signal transducers and activators of transcription (JAK-STAT), Crk, insulin receptor substrate (IRS) signaling, and mitogen-activated protein (MAP) kinase pathways.[12] Through these pathways, the transcription of target proteins leads to immune and anti-tumor effects that might be associated with IFN-induced thyroiditis. IFN-α can induce over-expression of major histocompatibility complex (MHC) class I antigen on thyroid epithelial cells, which switches the immune response to the Th1 pattern thereby stimulating an inflammatory

Table 1. Summaries of multi-phasic thyroiditis in five cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Reference	Bohbot et al.[10]	Bohbot et al.[10]	Bohbot et al.[10]	Kim et al.[9]	Tran[3]
Sex/Age	M/41	M/39	M/47	F/31	M/53
History of thyroid disease	None	None	None	None	None
Duration of IFN-α	12 months	13 months	7 months	12 months	12 months
Phase	Tri-phasic	Tri-phasic	Tri-phasic	Bi-phasic	Tri-phasic
Course (as mentioned in the case)	Silent thyroiditis followed by Graves' disease	Silent thyroiditis followed by Graves' disease	Silent thyroiditis followed by Graves' disease	Destructive thyroiditis followed by Graves' disease	Two peaks of thyrotoxicosis bisected by hypothyroidism
1st phase	Thyrotoxicosis	Thyrotoxicosis	Thyrotoxicosis	Thyrotoxicosis	Thyrotoxicosis
- Month to 1st	4 month	4 month	6 month	7 month	7 month
- Antibody: TPOAb/TgAb/TSHRAb	(-/+/-)	(+/ND/-)	(+/ND/-)	(-/-/-)	(+/-/-)
- Scintiscan	No uptake	No uptake	No uptake	No uptake	No uptake
2nd phase	Hypothyroidism	Hypothyroidism	Hypothyroidism	Thyrotoxicosis	Hypothyroidism
- Month to 2nd	5 month	6 month	8 month	14 month	9 month
3rd phase	Thyrotoxicosis	Thyrotoxicosis	Thyrotoxicosis	-	T3-Thyrotoxicosis
- Month to 3rd	9 month	8 month	11 month	-	14 month
Last finding					
- Antibody: TPOAb/TgAb/TSHRAb	(+/+/+)	(ND/ND/+)	(ND/ND/+)	(ND/+/+ → -)	(+/+/+)
- Scintiscan	Intense uptake	Intense uptake	Intense uptake	Intense uptake	Intense uptake
Treatment for thyroid +	ATD, B-blocker and LT4	ATD and LT4	ATD	B-blocker and ATD	B-blocker and ATD
IFN-α treatment	Continued	Discontinued	Discontinued	Continued	Continued

ATD: anti-thyroid drug, IIT: interferon induced thyroiditis, LT4: levothyroxine, ND: not done.
Normal range: Case 1-3 TSH (0.27-4.2 mIU/l), FT4 (9.3-17 ng/l), T3 (2.57-4.43 ng/l); Case 4 TSH (0.35-5.5 mIU/l), FT4 (9-26 pM/l), T3 (1.1-2.9 nM/l), Total T4 (64-154 Nm/l); Case 5 TSH (0.4-4.0 mIU/l), FT4 (10.1-24.5 pM/l), T3 (3.3-5.9 pmol/l).

response and tissue damage.[13,14] IFN can cause thyroid autoimmunity *de novo* or exacerbate pre-existing thyroid autoimmunity.[2] The incidence of the *de novo* development of thyroid antibody is 10-40%,[15,16] and the majority of patients remain positive when the treatment course is completed.[17] The most common clinical manifestation of IIT is Hashimoto's thyroiditis. Approximately 45-60% of patients with pre-existing thyroid antibodies are likely to develop Hashimoto's thyroiditis, while only 3-5% of those without circulating antibodies before IFN treatment develop the disease.[9] Graves' disease is a less common manifestation of autoimmune IIT. Wong et al.[18] reported that 10 of 321 patients with IFN-α developed thyrotoxicosis; only six of these cases were consistent with Graves' disease. Lisker-Melman et al.[19] reported that 2 of 327 patients on IFN-α treatment were diagnosed with Graves' disease that required treatment. The majority of IFN-induced Graves' disease cases require prolonged treatment with anti-thyroid medications even after the IFN-α therapy is stopped.[16] In cases of mild Graves' disease, it is not necessary to stop IFN-α, and anti-thyroid drugs can be added at low-doses to control thyrotoxicosis. However, IFN-α-induced Graves' disease usually does not enter remission upon completion or cessation of IFN-α therapy and anti-thyroid drugs often aggravate liver dysfunction in patients with hepatitis. In these cases, radioiodine or thyroidectomy should be considered in the treatment of Graves' disease.[20]

In summary, IFN-α can induce a broad spectrum of IIT. Here, we report a case that showed a bi-phasic swinging pattern of thyroiditis with severe destructive hypothyroidism followed by Graves' disease. This case will contribute to our understanding of the pathogenesis of IIT, a rare but important adverse effect of interferon treatment.

References

1) Mao XR, Zhang LT, Chen H, Xiao P, Zhang YC. *Possible factors affecting thyroid dysfunction in hepatitis C virus-infected untreated patients. Exp Ther Med 2014;8(1):133-40.*
2) Mandac JC, Chaudhry S, Sherman KE, Tomer Y. *The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology 2006;43(4):661-72.*
3) Tran HA. *The swinging thyroid in hepatitis C infection and interferon therapy. QJM 2010;103(3):187-91.*
4) Tomer Y, Menconi F. *Interferon induced thyroiditis. Best Pract Res Clin Endocrinol Metab 2009;23(6):703-12.*
5) Barut Ş, Günal Ö. *Thyroid disorders associated with hepatitis C or interferon based therapies. J Microbiol Infect Dis 2013; 3(3):147-9.*
6) Jadali Z. *Autoimmune thyroid disorders in hepatitis C virus infection: effect of interferon therapy. Indian J Endocrinol Metab 2013;17(1):69-75.*
7) Caraccio N, Cuccato S, Pratesi F, Dardano A, Ursino S, Chimenti D, *et al. Effect of type I interferon(s) on cell viability and apoptosis in primary human thyrocyte cultures. Thyroid 2009;19(2):149-55.*
8) Akeno N, Smith EP, Stefan M, Huber AK, Zhang W, Keddache M, *et al. IFN-alpha mediates the development of autoimmunity both by direct tissue toxicity and through immune cell recruitment mechanisms. J Immunol 2011; 186(8):4693-706.*
9) Kim BK, Choi YS, Park YH, Lee SU. *Interferon-alpha-induced destructive thyroiditis followed by Graves' disease in a patient with chronic hepatitis C: a case report. J Korean Med Sci 2011;26(12):1638-41.*
10) Bohbot NL, Young J, Orgiazzi J, Buffet C, Francois M, Bernard-Chabert B, *et al. Interferon-alpha-induced hyperthyroidism: a three-stage evolution from silent thyroiditis towards Graves' disease. Eur J Endocrinol 2006;154(3):367-72.*
11) Savvas SP, Papakostas N, Giannaris M, Malaktari S, Koskinas J, Archimandritis AJ. *Interferon alpha-induced hashimoto thyroiditis followed by transient graves disease in a patient with chronic HCV infection. South Med J 2010;103(6):585-8.*
12) Parmar S, Platanias LC. *Interferons: mechanisms of action and clinical applications. Curr Opin Oncol 2003;15(6):431-9.*
13) Roti E, Minelli R, Giuberti T, Marchelli S, Schianchi C, Gardini E, *et al. Multiple changes in thyroid function in patients with chronic active HCV hepatitis treated with recombinant interferon-alpha. Am J Med 1996;101(5):482-7.*
14) Farrar JD, Murphy KM. *Type I interferons and T helper development. Immunol Today 2000;21(10):484-9.*
15) Watanabe U, Hashimoto E, Hisamitsu T, Obata H, Hayashi N. *The risk factor for development of thyroid disease during interferon-alpha therapy for chronic hepatitis C. Am J Gastroenterol 1994;89(3):399-403.*
16) Preziati D, La Rosa L, Covini G, Marcelli R, Rescalli S, Persani L, *et al. Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. Eur J Endocrinol 1995;132(5):587-93.*
17) Carella C, Mazziotti G, Morisco F, Manganella G, Rotondi M, Tuccillo C, *et al. Long-term outcome of interferon-alpha-induced thyroid autoimmunity and prognostic influence of thyroid autoantibody pattern at the end of treatment. J Clin Endocrinol Metab 2001;86(5):1925-9.*
18) Wong V, Fu AX, George J, Cheung NW. *Thyrotoxicosis induced by alpha-interferon therapy in chronic viral hepatitis. Clin Endocrinol (Oxf) 2002;56(6):793-8.*
19) Lisker-Melman M, Di Bisceglie AM, Usala SJ, Weintraub B, Murray LM, Hoofnagle JH. *Development of thyroid disease during therapy of chronic viral hepatitis with interferon alfa. Gastroenterology 1992;102(6):2155-60.*
20) Carella C, Mazziotti G, Amato G, Braverman LE, Roti E. *Clinical review 169: Interferon-alpha-related thyroid disease: pathophysiological, epidemiological, and clinical aspects. J Clin Endocrinol Metab 2004;89(8):3656-61.*