INTERNAL MEDICINE

□ CASE REPORT □

A Case of Type 1 Diabetes Onset and Recurrence of Graves' Disease During Pegylated Interferon-Alpha Plus Ribavirin Treatment for Chronic Hepatitis C

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Abstract

We report a case of type 1 diabetes onset and recurrence of Graves' disease during pegylated interferon (PEG-IFN)-alpha plus ribavirin treatment for chronic hepatitis C. The patient was a 55-year-old woman diagnosed with chronic hepatitis at age 46 years. She was treated for Graves' disease at 50 years of age. Because Graves' disease remitted, PEG-IFN-alpha plus ribavirin treatment was started for chronic hepatitis C. She was examined because of complaints of general fatigue, weight loss, and palpitations after 24 weeks of the treatment. She was diagnosed with a recurrence of Graves' disease, and methimazole treatment was started. However, she complained of malaise, thirst, polyuria, and loss of body weight. Her fasting blood glucose level was 292 mg/dL and HbA1c was 9.3%. Serum anti-GAD (glutamic acid decarboxylase) antibodies were 2.2 U/mL. She was diagnosed with type 1 diabetes with ketosis, and insulin treatment was started. Serum anti-GAD antibodies gradually increased to 15.1 U/mL. Graves' disease and type 1 diabetes are often complicated, and the coincidental occurrence of these 2 diseases is known as autoimmune polyglandular syndrome type III. However, only a few cases have shown that these diseases occur after IFN treatment.

Key words: Basedows' disease, TSH receptor antibodies, HLA, autoimmune polyglandular syndrome

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Introduction

Interferon (IFN) therapy is the only causal therapy used to eliminate hepatitis C virus directly when treating chronic hepatitis C (1). Recently, it has become possible to use prolonged administration and re-administration of IFN in patients with chronic hepatitis C, and IFN therapy has become popular by the introduction of pegylated interferon (PEG-IFN) and the establishment of PEG-IFN plus ribavirin combination therapy in Japan. PEG-IFN plus ribavirin combination therapy has become the mainstream therapy, and its effectiveness has improved (2). However, severe side effects of IFN therapy have been reported, including fever, arthralgia, thrombocytopenia, and leukocytopenia. IFN exerts antitumor activity, cytostatic activity and immunoregulatory effect, and antiviral activity (3). In addition, animals administered ribavirin show enhancement of autoimmune reaction (4). Thus, the combination of IFN and ribavirin may induce autoimmune-related disorders, type 1 diabetes, autoimmune thyroid disease, systemic lupus erythematosus (SLE), and rheumatoid arthritis (5-8). Graves' disease and type 1 diabetes are considered in relation to organ-specific autoimmune disease. Here, we describe a case of new onset of type 1 diabetes and recurrence of Graves' disease during PEG-IFN-alpha plus ribavirin treatment in a patient with chronic hepatitis C.

Case Report

A 55-year-old Japanese woman was admitted to our hospital in July 2007 complaining of symptoms including thirst,

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Table 1. Laboratory Data on Admission

Peripheral blood			BUN	9.9	mg/dL	Endocrinological data	
WBC	2900	/μL	Cr	0.4	mg/dL	TSH	0.02 μIU/mL
RBC	421×10⁴	/μL	UA	3.4	mg/dL	freeT$_3$	1.88 pg/mL
Hb	12.4	g/dL	Na	138	mEq/L	freeT$_4$	0.62 ng/dL
Ht	37.6	%	K	4.3	mEq/L	TGHA	<100×
Plt	14.5×10⁴	/μL	Cl	104	mEq/L	MCHA	6400×
Blood chemistry			Ca	9.0	mg/dL	TSAb	474 %
T.Bil	0.7	mg/dL	Ketone	4270	μmol/L	ACTH	11.2 pg/mL
ALT	25	IU/L	Diabetic data			cortisol	8.7 μg/dL
AST	19	IU/L	FPG	291	mg/dL	GH	4.75 ng/mL
LDH	173	IU/L	HbA1c	9.3	%	IGF-1	64 ng/mL
ALP	342	IU/L	CPR	0.4	ng/mL	LH	12.90 mIU/mL
γ-GTP	12	IU/L	Anti-GAD Ab	2.2	U/mL	FSH	43.26 mIU/mL
TP	7.2	g/dL	IA-2 Ab	<0.4	U/mL	PRL	4.14 ng/mL
Alb	4.0	g/dL	Insulin Ab	7.5	%	HLA-A, B	
AMY	58	IU/L	Urinalysis			A33, A24, B44, B54	
CPK	70	IU/L	protein	(-)		HLA haplotype	
LDL-C	43	mg/dL	glucose	(3+)		DRB1* 0405 DRB1* 1302	
TG	163	mg/dL	ketone	(2+)		DQA1* 0303 DQA1* 0102	
HDL-C	26	mg/dL	CPR	13.2	μg/day	DQB1* 0401 DQB1* 0604	
			24hr Ccr	114.6	mL/min		

polyuria, general fatigue, and loss of body weight that had persisted for about 2 weeks. At age 32 years, she had received a blood transfusion during delivery. She was diagnosed with chronic hepatitis C virus infection in 1997. Serum HCV-RNA was positive (340 KIU/mL), and the genotype was 1b. She was diagnosed with Graves' disease and was treated with methimazole (MMI) in 2004. In 2006, her thyroid function was normalized and her TSH receptor antibody (TRAb) was negative; hence, MMI treatment was stopped. She had no history of diabetes mellitus (DM) and no family history of DM or autoimmune thyroid disease. She was started on PEG-IFN-alpha (80 μg subcutaneously, once weekly) plus ribavirin (800 mg/day, orally) in November 2006. After 24 weeks of treatment, she was examined following complaints of general malaise, weight loss, and palpitations. Thyroid function tests showed the following results: TSH, <0.01 μIU/mL; free triiodothyronine, 8.06 pg/mL; free thyroxine, 2.32 ng/dL; and TRAb, 65.9 IU/L. The patient was diagnosed with recurrence of Graves' disease and was started with 15 mg/day of MMI. In July 2007, she was admitted to Mishuku Hospital with complaints of experiencing malaise, thirst, polyuria and loss of body weight for 2 weeks. On admission, her height, weight, and body temperature were 152.8 cm, 45.8 kg, and 36.9℃, respectively. Her blood pressure was 131/93 mmHg, and pulse rate was 92 beats/min with regular rhythm. The mild diffuse goiter was palpable. Vitiligo of the skin and epilation of the scalp were not observed. Laboratory data on admission are shown in Table 1. When admitted to our hospital, her fasting blood glucose level was 292 mg/dL and HbA1c was 9.3%. Anti-GAD (glutamic acid decarboxylase) antibodies and IA-2 antibodies were 2.2 U/mL and <0.4 U/mL, respectively. She was diagnosed with type 1 diabetes with ketosis and was immediately started on insulin treatment. Her blood glucose levels were controlled with 22 units of insulin per day. Serum anti-GAD antibodies were gradually elevated to 15.1 U/mL, and her insulin requirement increased. Serum anti-GAD antibodies showed a tendency to decline when PEG-IFN plus ribavirin treatment was stopped, but serum CPR was persistent at low levels and her insulin requirement was 46 units per day. Her clinical course is described in Fig. 1.

Discussion

In the present case, new onset of type 1 diabetes and recurrence of Graves' disease were observed following PEG-IFN-alpha plus ribavirin treatment for chronic hepatitis C. It is well known that autoimmune disorders develop following IFN treatment (5-8). IFN has been reported to exert antitumor activity, cytostatic activity and immunoregulatory effects, and antiviral activity (3). In addition, ribavirin enhances autoimmune effects in animals (4). Thus, the combination therapy of IFN and ribavirin may induce autoimmunity-related disease, type 1 diabetes, autoimmune thyroid disease, and SLE (5-8). The present patient had a history of Graves' disease; however, anti-GAD antibodies and TRAb were negative, and fasting blood glucose level was normal before PEG-IFN plus ribavirin therapy. She developed a recurrence of Graves' disease and type 1 diabetes, and TRAb and anti-GAD antibodies were positive (at 6 and 7 months, respectively) after the commencement of PEG-IFN-alpha plus ribavirin combination therapy. Therefore, it is suspected that PEG-IFN plus ribavirin therapy may influence the development of these diseases.

It is reported that autoimmune thyroid disease is often complicated by IFN therapy, and the incidence is reported to be approximately 2-9%; the incidence of Hashimoto disease, silent thyroiditis, and Graves' disease is 62%, 16%, and 11%, respectively (6). Thyrotoxicosis following IFN is generally transient because it is almost always associated with painless thyroiditis, and Graves' disease is rare. In our patient, it is thought that the cause of thyrotoxicosis was

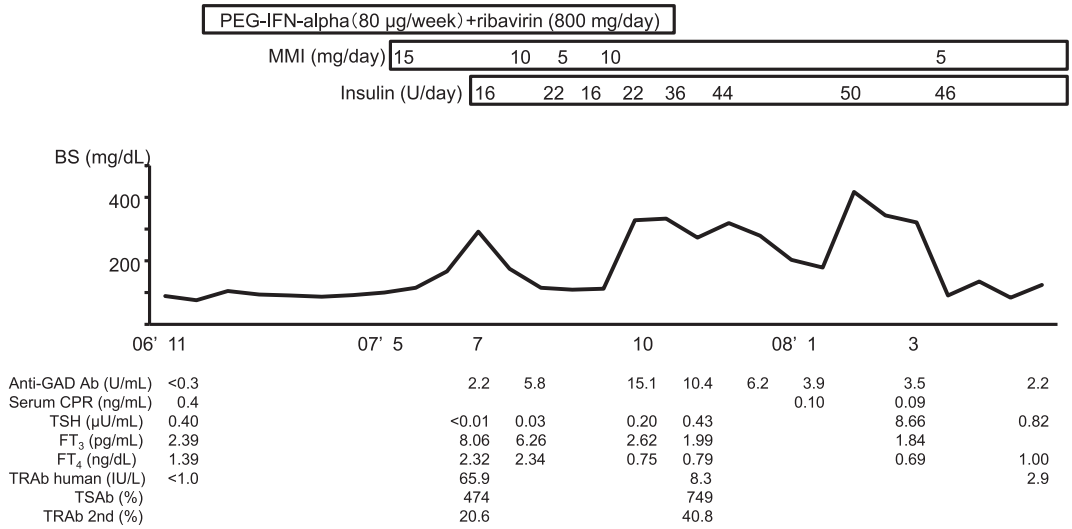

Figure 1. Clinical course of our patient. Serum anti-GAD antibodies were gradually elevated during PEG-IFN plus ribavirin treatment. When the treatment was discontinued, the antibodies showed a declining tendency.

Graves' disease, because TRAb and TSAb were positive both pre- and post treatment.

The mechanism for autoimmune thyroid disorders resulting from IFN therapy is unknown; however, several possible reasons have been suggested. One possible reason is that IFN-alpha induces overexpression of MCH class I antigens on the surface of thyroid epithelial cells (9). This overexpression is associated with the activation of cytotoxic T cells and induced destruction of thyroid tissue. IFN-alpha also causes an immune response shift to T-helper (Th) 1 predominance through the production of cytokines such as IL-2 or IFN-gamma, thereby creating predisposition to autoimmune thyroid disease (10, 11). While the mechanism for Graves' disease after IFN therapy is unclear, it is generally known that Graves' disease may involve Th2 dominance (12). Recently, it has been suggested that the initiation of Graves' disease is likely mediated by Th1 lymphocytes, and this fact may be associated with the occurrence of Graves' disease due to IFN-alpha treatment (13). On the other hand, it is reported that antithyroid antibodies are high in patients with chronic hepatitis C (7). This finding raises the possibility that hepatitis C virus infection induces an autoimmune reaction in the thyroid gland.

The frequency of newly onset diabetes following IFN therapy is reported to be 0.08-0.7% (14, 15). However, previous studies have not examined pancreatic antibodies such as anti-GAD antibody, IA-2 antibody, or ICA, thus making clear differentiation between type 1 and type 2 diabetes impossible. Thus, the frequency of newly onset type 1 diabetes following IFN therapy is uncertain. The pathogenesis of type 1 diabetes is not completely understood; however, immunologic, genetic, and environmental factors may contribute to the pathogenesis of type 1 diabetes. It is reported that IFN-alpha enhances the expression of MHC class I molecules in pancreatic beta cells, resulting in the activation of natural killer cells and T cells (16, 17). A pancreatic immunohistochemical examination of patients with type 1 diabetes revealed that immunoreactivity IFN-alpha confined by beta cells was found in 93% of pancreatic islet cells that overexpressed MHC class I molecules (17). However, it was not found in pancreatic islet cells in nondiabetic and type 2 diabetes patients. It is reported that diabetes developed in a transgenic mouse when IFN-alpha genes were introduced into pancreatic beta cells, and that it was inhibited by the administration of anti-IFN-alpha antibodies (18). These results suggest that IFN-alpha may play an important role in the development of type 1 diabetes.

Graves' disease and type 1 diabetes are often complicated, and the coincidental occurrence of these 2 diseases is known as autoimmune polyglandular syndrome (APS) type III (19). However, only 1 case has been reported, where Graves' disease and type 1 diabetes developed concurrently after IFN treatment (20). In that case, it was not clear whether anti-GAD antibody and TRAb were induced by IFN because autoantibodies were not examined prior to treatment. However, in the present case, we confirmed that the anti-GAD antibody and TRAb were absent before IFN treatment and present during treatment. The mechanism of APS type III is unknown but is suspected to be strongly associated with HLA class II. Recently, it has been reported that susceptibility alleles and haplotypes of HLA class II are strongly associated with APS type III in Japanese individuals (21). In APS III patients with Graves' disease and type 1 diabetes, the haplotype frequencies of HLA DRB1*0405-DQA1*0303-DQB1*0401, and DRB1*0802-DQA1*0301-DQB1*0302 were significantly higher than in controls. Interestingly, DNA-based typing for the HLA haplotype revealed the haplotype HLA DRB1*0405-DQA1*0303-DQB1*0401, thereby suggesting that the patient was genetically susceptible to the APS type III with Graves' disease and type 1 diabetes. In addition, the previous case showed DRB1*0405-DQA1*0303-DQB1*0401. Given the existence

of susceptible genes of APS type III, the combination of Graves' disease and type 1 diabetes was not coincidental, and was likely activated by IFN-alpha plus ribavirin therapy.

The present patient had HLA A-24. The destruction of beta cells in the pancreas is promoted in patients with HLA-A24 (22). Despite fasting blood glucose levels being measured at regular intervals, the patient presented with ketosis at the time of diagnosis of diabetes, and endogenous insulin secretion having been exhausted rapidly subsequently in the present case, it may be associated with HLA-A24.

In conclusion, we report here a case of new onset of type 1 diabetes and recurrence of Graves' disease during PEG-IFN-alpha plus ribavirin treatment in a patient with chronic hepatitis C. PEG-IFN plus ribavirin combination therapy may induce autoimmune disease to a greater extent than IFN monotherapy. We recommend the regular measurement of blood glucose, thyroid hormone, and autoantibody levels, both prior to and during IFN therapy, in order to establish the occurrence of autoimmune disease.

References

1. Di Bisceglie AM, Martin P, Kassianides C, et al. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. N Engl J Med **321**: 1506-1510, 1989.
2. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet **358**: 958-965, 2001.
3. Vial T, Descotes J. Clinical toxicity of the interferons. Drug Saf **10**: 115-150, 1994.
4. Lau JY, Tam RC, Liang TJ, Hong Z. Mechanism of action of ribavirin in the combination treatment of chronic HCV infection. Hepatology **35**: 1002-1009, 2002.
5. Dusheiko G. Side effects of alpha interferon in chronic hepatitis C. Hepatology **26** (Suppl 1): 112S-121S, 1997.
6. Nagayama Y, Ohta K, Tsuruta M, et al. Exacerbation of thyroid autoimmunity by interferon α treatment in patients with chronic viral hepatitis: our studies and review of the literature. Endocr J **41**: 565-572, 1994.
7. Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology **43**: 661-672, 2006.
8. Chung RT, Gale M Jr, Polyak SJ, Lemon SM, Liang TJ, Hoofnagle JH. Mechanisms of action of interferon and ribavirin in chronic hepatitis C: Summary of a workshop. Hepatology **47**: 306-320, 2008.
9. Saji M, Moriarty J, Ban T, Singer DS, Kohn LD. Major histocompatibility complex class I gene expression in rat thyroid cells is regulated by hormones, methimazole, and iodide as well as interferon. J Clin Endocrinol Metab **75**: 871-878, 1992.
10. Farrar JD, Murphy KM. Type 1 interferons and T helper development. Immunol Today **21**: 484-489, 2000.
11. Tilg H. New insights into the mechanisms of interferon alfa: an immunoregulatory and anti-inflammatory cytokine. Gastroenterology **112**: 1017-1021, 1997.
12. Land KJ, Moll JS, Kaplan MH, Seetharamaiah GS. Signal transducer and activator of transcription (Stat)-6-dependent, but not Stat4-dependent, immunity is required for the development of autoimmunity in Graves' hyperthyroidism. Endocrinology **145**: 3724-3730, 2004.
13. Nagayama Y, Mizuguchi H, Hayakawa T, Niwa M, McLachlan SM, Rapoport B. Prevention of autoantibody-mediated Graves' -like hyperthyroidism in mice with IL-4, a Th2 cytokine. J Immunol **170**: 3522-3527, 2003.
14. Fattovich G, Giustina G, Favarato S, Ruol A. A survey of adverse events in 11241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol **24**: 38-47, 1996.
15. Okanoue T, Sakamoto S, Itoh Y, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol **25**: 283-291, 1996.
16. Pujol-Borrell R, Todd I, Doshi M, et al. HLA class II induction in human islet cells by interferon-gamma plus tumour necrosis factor or lymphotoxin. Nature **326**: 304-306, 1987.
17. Foulis AK, Farquharson MA, Meager A. Immunoreactive alpha-interferon in insulin-secreting β cells in type 1 diabetes mellitus. Lancet **2**: 1423-1427, 1987.
18. Stewart TA, Hultgren B, Huang X, Pitts-Meek S, Hully J, MacLachlan NJ. Induction of type 1 diabetes by interferon-α transgenic mice. Science **260**: 1942-1946, 1993.
19. Eisembarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. N Engl J Med **350**: 2068-2079, 2004.
20. Hayashi M, Kataoka Y, Tachikawa K, Koguchi H, Tanaka H. Dual onset of type 1 diabetes mellitus and Graves' disease during treatment with pegylated interferon α-2b and ribavirin for chronic hepatitis C. Diabetes Res Clin Pract **86**: e19-e21, 2009.
21. Hashimoto K, Maruyama H, Nishiyama M, et al. Susceptibility alleles and haplotypes of human leukocyte antigen DRB1, DQA1, and DQB1 in autoimmune polyglandular syndrome type III in Japanese population. Horm Res **64**: 253-260, 2005.
22. Nakanishi K, Kobayashi T, Murase T, et al. Assoication of HLA-A24 with complete β-cell destruction in IDDM. Diabetes **42**: 1086-1093, 1993.