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CASE REPORT

Type 1 Diabetes Mellitus Associated with Pegylated Interferon-α Plus Ribavirin Treatment for Chronic Hepatitis C: Case Report and Literature Review

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Abstract: Combined pegylated interferon (PEG-IFN)+ribavirin (RBV) therapy has been used as a primary treatment for chronic hepatitis C. However, IFN-induced autoimmune disease, including type 1 diabetes mellitus, has been highlighted as one of the problems with this therapy. Here we report the case of a patient who developed type 1 diabetes mellitus during combined PEG-IFN+RBV therapy for hepatitis C but who showed no exacerbation of diabetes despite continued use of IFN. A 63-year-old man with chronic hepatitis C and a nonresponder to previous IFNα treatments, was admitted to our hospital because of excessive thirst, polydipsia, and polyuria 24 weeks after the start of PEG-IFNα+RBV therapy. High levels of blood glucose and glycosylated hemoglobin and low levels of C-peptide and immunoreactive insulin were observed. The serum antiglutamic acid decarboxylase antibody titer was 27,700 U/mL. We diagnosed IFN-induced type 1 diabetes mellitus; however PEG-IFNα+RBV therapy was continued for 48 weeks. Serum HCV remains negative five years after this treatment. Intensive insulin therapy was started immediately after the diagnosis of type 1 diabetes. Although the patient initially required 22 U/day of insulin, the dosage could be gradually reduced after completion of PEG-IFNα+RBV therapy and blood glucose remained well controlled. Prediction of onset of type 1 diabetes mellitus on the basis of baseline measurement of pancreas-associated autoantibodies is difficult. Therefore, it would be advisable to consider the possibility of onset of type 1 diabetes mellitus in all patients receiving IFN+RBV therapy.

Keywords: type 1 diabetes mellitus, pegylated interferon, ribavirin, hepatitis C

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Introduction

Interferon (IFN) exerts antiviral, antiproliferative, and immunomodulatory actions,[1] and is used extensively for the treatment of chronic hepatitis C (HCV). Ribavirin (RBV), an antiviral agent, has been reported to reinforce the therapeutic effect of IFN in patients with chronic HCV.[2] In recent years, combined pegylated interferon (PEG-IFN)+RBV therapy has been used as a primary treatment for chronic HCV. However, IFN-induced autoimmune disease has been highlighted as one of the problems with this therapy. In 1992, Fabris et al reported the case of a patient with HCV who developed type 1 diabetes mellitus following treatment with IFNα.[3] Since then, cases of type 1 diabetes mellitus associated with IFN monotherapy or combined IFN+RBV therapy have been reported sporadically. IFN therapy is usually discontinued when type 1 diabetes mellitus is diagnosed in these patients. However, a few cases in which IFN therapy was continued even after the diagnosis of type 1 diabetes mellitus have also been reported. We report here the case of a patient who developed type 1 diabetes mellitus during combined PEG-IFNα+RBV therapy for HCV, who showed no worsening of diabetes despite continued use of IFN.

Case Report

A 63-year-old man presented to our hospital with excessive thirst, polydipsia, and polyuria. He had been diagnosed as having acute hepatitis B at age 35 years, at which time a liver biopsy had resulted in massive bleeding requiring blood transfusion. At age 48 years, he was diagnosed as having chronic HCV (genotype 1b). IFNα therapy for chronic HCV was administered at ages 50 years and 60 years, but the treatment failed to achieve negative conversion of serum HCV-RNA.

At age 63 years, PEG-IFNα+RBV was administered, and serum HCV-RNA became negative eight weeks after the start of this treatment. From week 16 onwards, the fasting plasma glucose level began to rise gradually from 5.0 mmol/L to 9.9 mmol/L. During week 24, the patient began to complain of excessive thirst, polydipsia, and polyuria. The patient had never been found to have abnormal glucose tolerance before. There was no family history of diabetes mellitus.

Physical findings on admission were height 165 cm, body weight 66 kg, body mass index 24.2 kg/m^2, and blood pressure 120/72 mmHg. His consciousness level was normal. Examination of the heart, lungs, and abdomen was also normal. No abnormalities were detected on neurological examination.

Mild anemia was noted (red blood cell count and hemoglobin 379×10^4/μL and 11.2 g/dL, respectively), but there were no abnormalities of the other blood cell parameters. Fasting plasma glucose was 16.2 mmol/L, serum glycosylated hemoglobin was 10.0% (Japan Diabetes Society), and serum glycoalbumin was 39.3%. There were no abnormalities in serum electrolyte profile, liver function, or renal function. Microalbuminuria was noted (urinary albumin, 56.4 mg/gcreatinine). The C-peptide level was 0.68 ng/mL (normal 1.00–2.00 ng/mL), fasting immunoreactive insulin was 3.0 μU/mL(normal 3.06–16.9 μU/mL), and the serum antiglutamic acid decarboxylase antibody titer was markedly elevated at 27,700 U/mL (normal $<$ 1.5 U/mL). Based on these findings, a diagnosis of type 1 diabetes mellitus was made. HLA DNA typing revealed DRB1*0101/*0405, which was not inconsistent with the diagnosis of type 1 diabetes mellitus.

Because the patient had HCV genotype 1b, which needed 48 weeks of combined PEG-IFNα+RBV therapy,[4] the treatment was continued even after diagnosis of diabetes mellitus, until 48 weeks with careful observation of plasma glucose levels. Serum HCV remains negative five years after this treatment. Intensive insulin therapy was started immediately after the diagnosis for treatment of type 1 diabetes mellitus. The patient initially required 22 U of insulin per day (insulin glargine 10 U, insulin as part 4–4–4 U); however, the dosage could be gradually reduced after completion of PEG-IFN+RBV therapy. At present, plasma glucose is well controlled (glycosylated hemoglobin 5.7%–6.5%), with only 6 U of insulin aspart needed per day. Serum antiglutamic acid decarboxylase antibody titers also decreased gradually from the initial 27,700 U/mL to about 900 U/mL at four years after the diagnosis.

Discussion

It has been reported that insulin resistance may develop as a result of interference in intracellular insulin signaling by HCV proteins, mainly viaserine phosphorylation of IRS-1 and impairment of the downstream Akt signaling pathway.[5] According to a report by Mehta et al, the incidence of type 2 diabetes

mellitus is about three times higher in HCV-infected individuals than in noninfected individuals overthe age of 40 years.[6] In contrast it has also been reported that the incidence of type 1 diabetes mellitus as a complication is lower than that of type 2 diabetes mellitus.[7] It has also been reported that the pancreas-associated autoantibody (including antiglutamic acid decarboxylase antibody) positivity rate in HCV patients is 3% before the start of IFN therapy but increases to 7% thereafter.[1] Thus, IFN therapy seems to be associated with the onset of diabetes mellitus mediated by the autoimmune system. Whether or not the type 1 diabetes mellitus that developed in the present case was associated with IFN+RBV therapy is an interesting point. No evidence of development of diabetes mellitus was seen during the first two sessions of IFN therapy; however, considering that the blood glucose level began to rise four months after the administration of IFNα+RBV therapy, it is unlikely that this patient would developed diabetes mellitus before the start of this therapy, and the most reasonable interpretation would be that the IFNα+RBV therapy was causatively associated with the onset of type 1 diabetes mellitus. Because pancreas-associated autoantibodies had not been measured before the start of IFNα+RBV therapy, it is unknown whether the timing of the start of this therapy coincided with onset of type 1 diabetes mellitus or whether the patient had developed slowly progressive type 1 diabetes before the start of the IFNα+RBV.

Twenty-eight cases of type 1 diabetes mellitus diagnosed after the start of IFN+RBV therapy have thus far

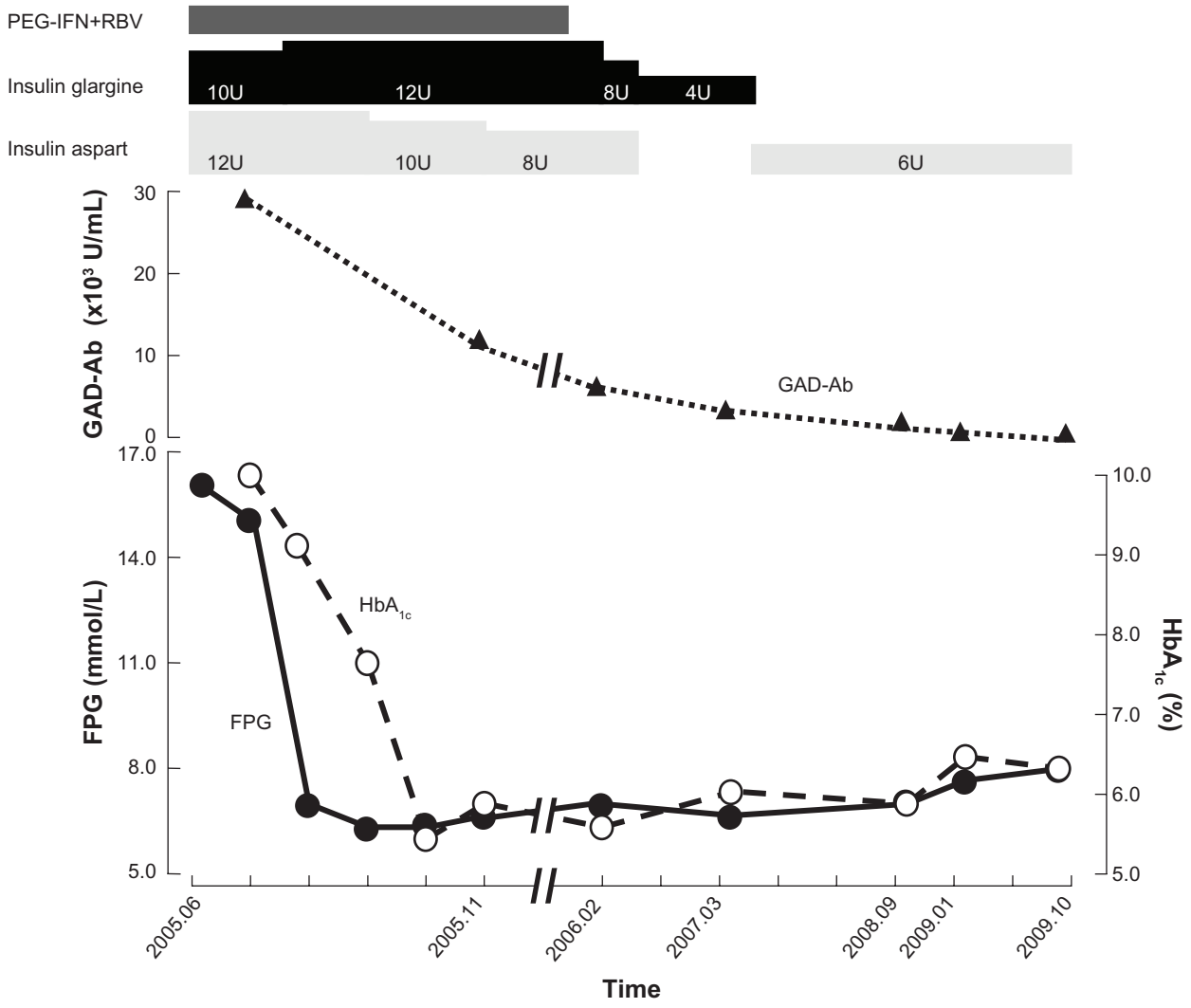

Figure 1. Clinical course of this patient.
Abbreviations: FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin (Japan Diabetes Society); Ab,antibody.

Table 1. Main clinical, immunological and genetic features of 28 patients with chronic type C viral hepatitis who developed type 1 diabetes mellitus associated with interferon treatment.

Case	Age	Gender	Latency before T1DM (month)	Continue of IFN	Improvement of DM after withdrowal of IFN	Anti-islet antibody		Type of IFN	HLA typing	Ref
						Before IFN treatment	After IFN treatment			
1	61	M	6	(–)	Nimp	(+)	(+)	α2b	DRB1*0401/*1101, DQB1*0502/0503	3
2	59	F	4	(–)	Imp	ND	(+)	α	DR4	8
3	29	M	5	(–)	Nimp	(+)	(+)	α2b	DRB1*04/*08, DQB1 57N-Asp/Asp	9
4	57	M	4	(–)	Nimp	(–)	(+)	α2b	DRB1*0405/*1401, DQB1*0401/0503	10
5	41	M	3	(–)	Nimp	(–)	(–)	α2b+REV	DRB1*0101/*0401	11
6	36	F	3	(–)	Nimp	(+)	(+)	α2b+REV	ND	11
7	29	M	8.5	(–)	Nimp	(–)	(+)	α	DRB1*0301, DQB1*0201	12
8	37	M	7.5	(–)	Nimp	(+)	(+)	α2b+REV	DR1/3	13
9	53	F	5	(–)	Nimp	ND	(+)	α2b+REV	ND	14
10	40	F	6	(–)	Nimp	(+)	(+)	α2b+REV	DR4/7, DQ2/8	15
11	40	F	2	(–)	Nimp	(+)	(+)	α2b+REV	ND	15
12	61	M	3	(–)	Nimp	(+)	(+)	PEG-α2b+REV	DRB1*04/*14, DQB1*04/*0503	16
13	42	F	2	ND	Nimp	(–)	(+)	PEG-α2b+REV	DR1/4, DQ2/5	17
14	38	F	4	(–)	Nimp	ND	(+)	PEG-α2a+REV	DRB1*03, DQB1*02	18
15	54	M	4 after IFN	ND	ND	(±)	(±)	PEG-α+REV	DR3	19
16	46	M	3	ND	ND	(+)	(+)	PEG-α+REV	ND	19
17	25	M	4 after IFN	ND	ND	(–)	(+)	PEG-α+REV	DR3, DQ2	19
18	44	F	5.5	ND	ND	(–)	(+)	PEG-α+REV	DR3/4, DQ2	19
19	46	M	4.5	ND	ND	(+)	(+)	PEG-α+REV	ND	19
20	51	M	6	(–)	Nimp	(–)	(+)	PEG-α2b+REV	ND	20
21	48	M	10	(–)	ND	(–)	(+)	PEG-α2b+REV	DRB1*0405/*0901, DQB1*0401/0303	21
22	65	M	12	(–)	ND	(–)	(+)	PEG-α2b+REV	DRB1*0410/*1407, DQB1*0402/0503	21
23	53	F	3	(–)	Nimp	ND	(+)	PEG-α+REV	DRB1*0405/0901, DQB1*0401/0303	22
24	46	F	13	(–)	Imp	ND	(+)	PEG-α2a+REV	DRB1*0405/0406, DQB1*0302/0401	23
25	67	F	4	(–)	Nimp	ND	(+)	PEG-α2a+REV	DRB1*0901/1302, DQB1*0303/0604	23

26	46	F	7	(–)	Nimp	ND	(+)	PEG-α2b+REV	DRB1*0407/0405, DQB1*0301/0303	24
27	55	F	6	(+)	Nimp	ND	(+)	PEG-α2a+REV	DRB1*0405/1302, DQB1*0401/0604	25
Our case	63	M	4	(+)	Nimp	ND	(+)	PEG-α+REV	DRB1*0101/*0405	

Abbreviations: T1DM, type1 diabetes mellitus; IFN, interferon; M, male; F, female; ND, not determined; Nimp, no improvement; Imp, improvement; PEG, peg-interferon; REV, ribavirin.

been reported in the English language literature.[3,8–25] We reviewed the data for each of these cases, focusing on the length of time from the start of IFN+RBV therapy to the onset of type 1 diabetes mellitus, continuation/discontinuation of IFN therapy after the onset of type 1 diabetes, weaning/nonweaning from insulin therapy after discontinuation of IFN+RBV, presence/absence of pancreas-associated autoantibodies before and after IFN+RBV therapy, and the HLA haplotype of the patients (Table 1). While in most cases IFN+RBV therapy had been discontinued immediately after the diagnosis of type 1 diabetes,[3,8–16,18,20–24] the treatment had been continued in two cases, including the present case.[25] Insulin therapy could be discontinued later in only two of the 19 cases in which IFN+RBV therapy had been stopped immediately after the diagnosis of type 1 diabetes.[8,23] Weaning from insulin therapy appears to be difficult in cases of type 1 diabetes mellitus developing after the start of IFN+RBV therapy, and it has been reported that weaning was impossible in 75% of such cases.[1] A report of cases of type 1 diabetes mellitus developing after completion of IFN+RBVtherapy[19] suggests that discontinuation of IFN+RBV therapy does not always suppress the onset of type 1 diabetes mellitus. After the onset of type 1 diabetes, insulin secretion was improved three months later by strict control of diabetes in case 2, and insulin treatment could be canceled 14 months later in case 24. Therefore, if strict blood glucose control is possible regardless of continuation/discontinuation of IFN+RBV therapy, it would seem possible to reduce the insulin dose required eventually, as achieved in the present case (probably the so-called "honeymoon phenomenon"). In this sense, strict control of diabetes is essential when dealing with such cases.

As shown in Table 1, among the 28 reported patients, 19 had undergone measurement of pancreas-associated autoantibodies before the start of IFN-RBV therapy,[3,9–13,15–17,19–21] which revealed 10 antibody-positive cases[3,9,11,13,14,16,19] and nine antibody-negative cases.[10–12,17,19–21] On the other hand, after the start of treatment, autoantibodies were positive in 27 of the 28 cases. Autoantibodies remained negative in only one case; however, a diagnosis of type 1 diabetes mellitus was made on the basis of the clinical course and capacity for insulin secretion.[11] Although checking for pancreas-associated

autoantibodies before the start of IFN+RBV therapy may seem valid, it would appear to be difficult to predict the onset of type 1 diabetes mellituson the basis of the results. Rather than checking for pancreas-associated autoantibodies, checking for the HLA haplotype before the start of this therapy may be more useful to predict the onset of type 1 diabetes mellitus, in view of reports that the HLA haplotype may be closely involved in the onset of type 1 diabetes mellitus associated with IFN+RBV therapy.[1,19] However, because checking of the HLA haplotype is an expensive investigation and type 1 diabetes mellitus is a rare complication of IFN+RBV therapy, it may be difficult to perform this test in all cases. It would therefore be advisable to bear in mind the possibility of onset of type 1 diabetes mellitus when IFN+RBV therapy is administered.

IFN causes a shift in the Th1/Th2 balance to a Th1-predominant state, which results in induction of Th1-type cytokines, such as IFN-γ and interleukin 2. These cytokines activate macrophages, natural killer cells, and cytotoxic T lymphocytes, resulting in exaggerated cellular immune responses.[1,26,27] The Th1-predominant state also seems to amplify autoimmune responses, accelerating β cell destruction in the pancreas. Alternatively, it is possible that Th1-type cytokines induce the Fas antigen on the β cell surface, resulting in cellular apoptosis, or that free radicals formed by the actions of cytokines serve as cytotoxic factors for β cells.[28,29] RBV also has the effect of causing a shift in the Th1/Th2 balance to a Th1-predominant state, reinforcing IFN-induced activation of cellular immunity in a synergistic manner.[30] In the present case, three sessions of IFN+RBV therapy were administered; however, hyperglycemia was not noted during the first two sessions. Although it is highly probable that addition of RBV to IFN therapy caused the onset of type 1 diabetes mellitus in the present case, further data is needed to examine whether or not IFN+RBV therapy might be associated with an elevated risk of developing type 1 diabetes mellitus as compared with use of IFN therapy alone.

Conclusion

We encountered a patient who was diagnosed as having type 1 diabetes mellitus during combined PEG-IFNα+RBV therapy, in whom no aggravation of diabetes was found despite continued use of IFNα+RBV therapy. Prediction of the onset of type 1 diabetes mellitus is difficult based on the baseline measurement of pancreas-associated autoantibodies alone. Therefore, it would be advisable to bear in mind the possibility of onset of type 1 diabetes mellitus in all patients treated with IFN+RBV.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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