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Acute Exacerbation of Liver Disease Induced by Pegylated Interferon Alpha2a Treatment for Chronic Hepatitis C

Hideaki Kato, Hirokazu Ikeuchi, Makoto Nakamura

[1]Department of Gastroenterology, Toyokawa City Hospital, Toyokawa, Japan.
Email: hideakik@k6.dion.ne.jp

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ABSTRACT

A 66-year-old female was referred to a local clinic for the treatment of chronic hepatitis C. Her family physician started the administration of Peg-IFN alpha2a in combination with ribavirin in September, 2008. *Three months after the commencement of the therapy, alopecia was noted, and it gradually worsened. She also complained of general fatigue. Since her alopecia and general fatigue continued to worsen, her family physician decided to discontinue the Peg-IFN plus ribavirin therapy in February,* 2009. *On April* 5, *the patient complained of severe general fatigue as well as fever, and she was referred to the local clinic again. Blood chemistry tests demonstrated that her AST level increased from* 200 *IU on April* 5 *to* 1000 *IU on April* 9 *but her HCV RNA level stayed at* 4.1 *logIU/mL. Based on the findings of an elevated IgG level* (2244 *mg*), *AST/ALT* > 1.5, *and weak positivity for anti-smooth muscle antibody* (1:40), *an autoimmune mechanism was considered as the etiology of her liver damage. Despite treatment with* 60 *ml of glycyrrhizin,* 1 *g of gabexate mesylate, and* 500 *mg of methylprednisolone, she died on April* 23. *Peg-IFN induced acute liver failure is quite rare, but clinicians should aware of this life-threatening side effect during and after interferon therapy.*

***Keywords*:** *Adverse Effect, Autoimmune Hepatitis, Chronic Hepatitis C, Pegylated Interferon*

1. Introduction

The administration of pegylated interferon (Peg-IFN) in combination with ribavirin is currently the first-line option for the treatment of chronic hepatitis. This approach achieves a sustained virological response in more than 90% of patients with genotype 2 and a low viral load and in approximately 60% of the patients with genotype 1b and a high viral load [1]. During IFN therapy, various types and degrees of adverse effects are observed. Thrombocytopenia, interstitial pneumonia, and depression are known to be life-threatening side effects of IFNα [1-3]. It is also known that IFNαinduces autoimmune disease and activates subclinical autoimmune diseases, such as thyroiditis, hemolytic anemia, and autoimmune hepatitis [4]. IFNα-induced acute exacerbation of liver disease leading to jaundice is extremely rare [5,6]. Here, we report a case of Peg-IFN alpah2a plus ribavirin therapy induced liver failure in which an auto-immune mechanism was considered as its etiology.

2. Case

A 66-year-old female was referred to a local clinic for the treatment of chronic hepatitis C. She had suffered from chronic hepatitis since she was 40 years old. Her past and family history were unremarkable, and she did not drink alcohol. Laboratory findings on referral showed an asparate aminotransferase (AST) level of 133 IU, an alanine aminotransferase (ALT) 161 IU/ml, a platelet count of $8.6 \times 10^4/\mu L$, a red blood cell count of $381 \times 10^4/\mu L$, a hemoglobin level of 11.8 g/dl, antinuclear antibody: negative, HCV serogroup: 1, and HCV RNA level: 4.5 logIU/ml. She was diagnosed with early stage liver cirrhosis, and her family physician decided to reduce her dose of Peg-IFNα2a to 90 μg and that of ribavirin to 400 mg. Treatment with the reduced doses of Peg-IFN and ribabirin was commenced in September, 2008 (**Figure 1**). After the first 3 months of the treatment, her platelet count and hemoglobin level had decreased to $5.0 \times 10^4/\mu L$ and 10.3 g/dL, respectively, but the combination therapy was continued without further reducing the dose of Peg-IFN or ribavirin. Three months after the commencement of the therapy, alopecia occurred and progressively worsened, and she also suffered from a general fatigue. Her alopecia and general fatigue continued to worsen, and

her family physician decided to discontinue the Peg-IFN plus ribavirin therapy in February, 2009. On April 5, the patient complained of severe general fatigue as well as fever and was referred to the local clinic again. Blood sampling tests demonstrated that her AST level increased from 200 IU on April 5 to 1000 IU on April 9, and the patient was transferred to our institute. A blood test on admission showed that her total bilirubin level and hepaplastin test result (normal 80-130%) were 3.7 mg/dL and 37%, respectively (**Table 1**), indicating severe her

Table 1. Laboratory findings on admission

(Blood cell count)			CRP	0.29	mg/dL
WBC	7000	/μL	IgG	2244	mg/dL
seg	72.7	%	IgA	241	mg/dL
lymph	16.6	%	IgM	182	mg/dL
mono	9.7	%	AFP	186	ng/mL
eos	0.4	%	PIVKA-II	95	mAU/mL
baso	0.6	%	CA19-9	615	IU/mL
RBC	386	$\times 10^4$/μL	CEA	1.6	ng/mL
hemoglobin	11.9	g/dl	RF	32	IU/mL
hematocrit	34.1	%	TSH	3.302	μIU/mL
PLT	8.4	$\times 10^4$/μL	f-T3	3.26	pg/mL
PT	15.1	second	f-T4	1.72	ng/mL
PT(%)	63	%	ANA	< 40	
APTT	1.23	second	AMA	−	
Fibrinogen	134.5	mg/dL	ASMA	40	
HPT	37	%	(Viral markers)		
NH_3	77	μg/dL	HBsAg	−	
(Biochemistry)			HCVAb	+	
TP	7.3	g/dL	HCV-RNA	4.1 logIU/mL	
Alb	3.3	g/dL	IgM HBcAb	−	
T.Bil	3.7	mg/dL	IgM HA Ab	−	
AST	1003	IU	HBsAb	320.5 mIU/mL	
ALT	496	IU	HBeAg	−	
LDH	356	IU	HBeAb	+	
ALP	328	IU	HBV DNA	−	
GTP	185	IU	HBcAb	17.8 s/co	
Blood sugar	100	mg/dL	CMV IgM(FA)	< 10	
BUN	9.4	mg/dL	CMV IgG(FA)	160	
Cre	1.0	mg/dL	EB-EA-DRIgG(FA)	< 10	
Na	132	mEq/L	EB-VCA IgM(FA)	< 10	
K	3.5	mEq/L	EB-VCAIgG(FA)	160	
Cl	101	mEq/L	EB-EBNA(FA)	80	
CPK	132	IU			
Fe	104	μg/dL			

Abbreviations; AFP, alpha feto-protein; Alb., albumin; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; APTT, activated partial thromboplastin time; AST, asparate aminotransferase; AT III, antithrombin III; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; CMV, cytomegalovirus; CPK, creatinine phosphokinase; Cre, serum creatinine; CRP, C-reacting protein; EB-EA-DR, Epstein-Barr virus Early Antigen-Diffuse and Restrict complex; EBNA, Epstein-Barr virus Nuclear Antigen; EB VCA, Epstein-Barr virus viral Capsid Antigen; FDP, fibrin/fibrinogen degradation products; GTP, glutamyl transpeptidase; HBc, hepatitis B core; HBe, hepatitis B e; HBs, hepatitis B surface; HCV, hepatitis C virus; HPT, hepaplastin test; LDH, lactate dehydrogenase; PIVKA-II, protein induced by vitamin K absence or antagonist; PLT, platelet count; PT, prothrombin time; RBC, red blood cell count; RF, rheumatoid factor; SFMC, soluble fibrin monomer complex; TP, serum total protein; TSH, thyroid stimulating hormone; WBC, white blood cell count.

liver dysfunction. Since HCV RNA level stayed 4.1 log IU/mL, worsening of her chronic hepatitis C was unlikely. The levels of other viral markers of liver damage were not significant. Therefore, autoimmune hepatitis induced by Peg-IFNα was most likely because of the findings of an ALP/AST ratio < 3.0, elevated IgG level of more than 2000 mg/dl, and the detection of antismooth muscle antibody (1:40). The administration of 60 ml of glycyrrhizin and 1 g of gabexate mesylate as well as 500 mg of methylprednisolone was commenced. A living-donor liver transplant was also prepared; however, the patient died on April 23. Autopsy was not allowed by her family.

3. Discussion

The side effects of Peg-IFNα plus ribavirin treatment are essentially universal and led to the dose reduction of interferon and/or ribavirin in 35-42% of patients treated with Peg-IFNα and the discontinuation of therapy in 14-19% of these patients [7,8]. Life-threatening side effects are quite rare; however, severe thrombocytopenia and interstitial pneumonia have sometimes resulted in fatalities [7,8]. Fattovich *et al*. investigated the frequency of severe adverse events after IFN therapy in a large, retrospective survey including 11,241 patients with chronic hepatitis B or C [9]. Among this large cohort, only 5 patients (0.04%) died because of therapy complications, and all five developed either liver failure or sepsis. Life-threatening side effects occurred in another 8 patients (0.07%), which included depression with a granulocyte count of less than 500/μL or a platelet count of less than 25,000/μL [9].

IFNα is known to sometimes induce or aggravate autoimmune diseases, such as thyroiditis and autoimmune hepatitis. It is reported that therapy with alpha IFN induces autoantibodies in more than half of patients treated for hepatitis C [10]. Interferon enhances the expression of HLA class I and II antigens on cell membranes, promoting T cell activation and the subsequent release of cytokines. A predominance of Th1 helper cells may favor organ-specific autoimmune phenomena [11,12]. The human leukocyte antigen haplotypes DR4, DR3, DR52, DQ2, and DR52 and DQ2 in combination are associated with disease exacerbation during interferon therapy (13).

In this case, an autoimmune mechanism activated by Peg-IFNα was considered to have caused the exacerbation of liver disease because of the following findings [1]; an elevated serum IgG level (2244 mg/dl) [2], ALP/AST > 3.0, and [3] weak positivity for anti-smooth muscle antibody (1:40). Disappointingly, in our patients, due to a

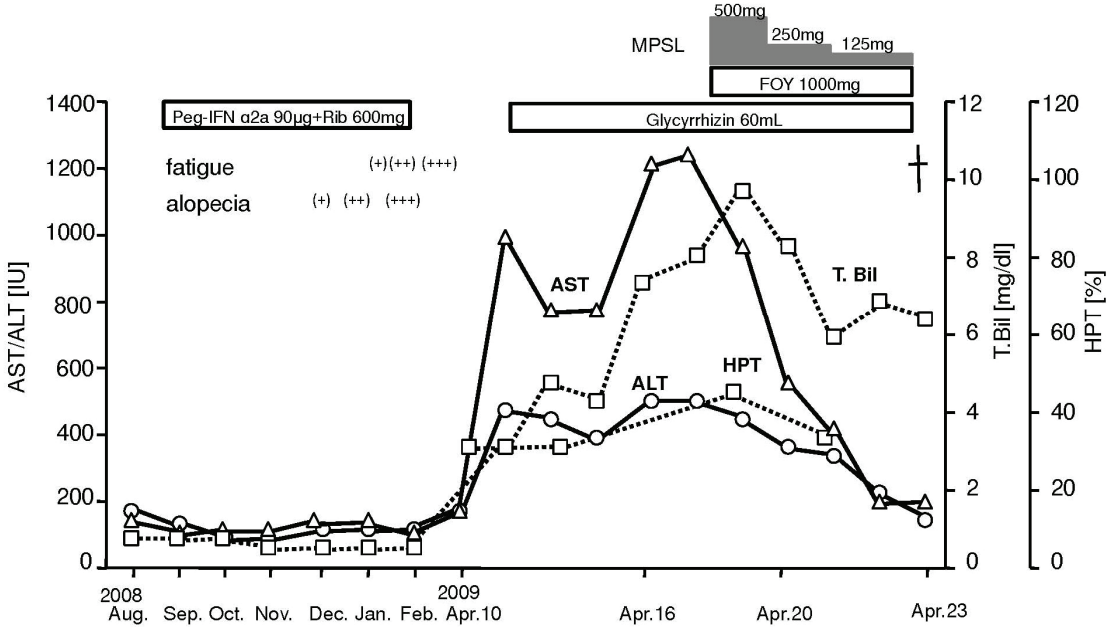

Figure 1. Clinical course the patient. The administration of pegylated interferon (Peg-IFN) alpha-2a in combination with ribavirin therapy was commenced in September 2008. Five months after the commencement of the therapy, the patients's alopecia worsened, she suffered from a general fatigue, and the Peg-IFN plus ribavirin therapy was discontinued. After the cessation of the Peg-IFN plus ribavirin therapy, her ALT level increased to 1000 IU and her hepaplastin test result (normal 70-130%) decreased to 37%. Glycyrrhizin, methylprednisolone, and gabexate mesylate were administered, but she died due to multi-organ failure. Abbreviations: AST, asparate aminotransferase; ALT, alanine aminotransferase; T.Bil, total bilirubin; HPT, hepaplastin test; Rib, ribavirin; FOY, gabexate mesylate; MPSL, methylprednisolone. The severity of fatigue and alopecia are shown as mild (+), moderate (++), or severe (+++).

lack of liver histology, the autoimmune scoring was not fully estimated. In our patient, autoimmune hepatitis score was calculated as 8 points; *i.e.*, 2 points less than the 10 point threshold indicating "probable autoimmune hepatitis".

Sezaki *et al*. reported 3 patients with chronic hepatitis C who developed jaundice during IFNα therapy. Of a total of 2,342 chronic hepatitis C patients treated with IFN in their institute, only 3 patients (0.1%) developed jaundice during or after IFN treatment, and they concluded that jaundice rarely develops in patients with hepatitis C during or after IFN therapy [6]. They also reported that the 3 patients had an autoimmune score of "probable AIH" prior to the initiation of IFN therapy and therefore that autoimmune scoring before IFN therapy would be a useful tool for predicting the development of autoimmune hepatitis [6]. However, in daily practice, it is not practical to investigate HLA haplotype and liver histology in all patients who undergo IFN therapy. Furthermore, in this patient, antinuclear antibody was negative at a screening blood test prior to IFN therapy. On the other hand, it was reported that up to 38% of patients with chronic hepatitis C show positivity for antinuclear antibody [14]. Moreover, patients with long-term chronic hepatitis C sometimes show a high IgG titer. These findings prevent us from detecting autoimmune hepatitis among patients with chronic hepatitis C. Therefore, clinicians should pay careful attention to their patients in an attempt to detect latent autoimmune hepatitis before the commencement of IFN therapy.

In this patient, the exacerbation of liver disease was noted after the cessation of IFN therapy. A similar phenomenon was observed in the case of Vispo *et al*. [15], and the exacerbation of liver disease was noted after the cessation of the treatment. In that case, the clinical course of the patient during IFN therapy was uneventful; however, 15 days after the cessation of Peg-IFNα2b plus ribavirin therapy, she complained of asthenia, arthralgia, myalgia and low-grade fever. Blood chemistry tests showed a 10-fold increase in her aminotransferase level. It is worth noting that the patient's autoimmune liver disease occurred after the cessation of IFN therapy. The mechanism of the time lag between IFN therapy and the development of liver damage is unknown; however, clinicians should pay attention to patients who complain of autoimmune disorder like symp toms, such as general fatigue, myalgia, and arthralgia after the completion of IFN treatment.

With regard to the treatment of autoimmune hepatitis induced by IFN, corticosteroid is reported to be effective [5,6,15]. In our patient, her ALT level began to decrease immediately after the administration of 500 mg of methylprednisolone, and her total bilirubin level also gradually decreased after the beginning of the therapy. However, the patient died without these levels ever recovering to within the normal range despite the steroid therapy. This dosen't show that steroids are ineffective for the treatment of autoimmune hepatitis induced by Peg-IFN because the cause of death of this patient was not exactly determined by pathological examination.

Although the incidence of IFN-induced autoimmune liver damage leading to jaundice is quite low, clinicians should be aware that Peg-IFNα plus ribavirin therapy has the potential to induce severe autoimmune liver failure. Clinicians should also carry out careful examinations of their patients regardless of whether they have an autoimmune disorder, before the commencement of Peg-IFNα plus ribavirin therapy. Further studies and the accumulation of data on Peg-IFN plus ribavirin therapy-induced autoimmune liver disease are required to elucidate the mechanism of this potentially life-threatening side effect and to develop the optimal treatment for this condition.

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