Title

Early detection of interstitial pneumonia by monitoring KL-6 in a chronic hepatitis C patient undergoing Peg-IFN and ribavirin therapy

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Running Titile: Effective monitoring for Peg-IFN and RBV-induced IP

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Abstract

A 58-year-old woman with chronic hepatitis C developed interstitial pneumonia (IP) while undergoing pegylated interferon (Peg-IFN) α2a and ribavirin (RBV) therapy. Serum levels of sialylated carbohydrate antigen KL-6 (KL-6), a known marker of disease activity in fibrosing lung disorders, had been regularly measured once a month for early detection of IP, and had begun rising noticeably from 12 weeks to 540 U/ml at 33 weeks of treatment. On examination, remarkable fine crackles were detected by dorsal auscultation and bilateral ground glass opacities and reticular shadows were depicted by computed tomography. The patient successfully recovered from her early stage pneumonia by immediate discontinuation of therapy, which indicates that regular monitoring of serum KL-6 may be effective for avoidance of IP progression induced by Peg-IFN and RBV therapy.

Key words: pegylated interferon, ribavirin, interstitial pneumonia, KL-6

INTRODUCTION

Pegylated interferon (Peg-IFN) α2a combined with ribavirin (RBV) has become one of the gold standards for hepatitis C virus (HCV) treatment [1]. However, side effects are observed in almost 80 percent of patients receiving this therapy. Pulmonary toxicity in patients undergoing HCV treatment is rare, especially interstitial pneumonia (IP) induced by Peg-IFN and RBV therapy. Sialylated carbohydrate antigen KL-6 (KL-6) is a mucinous high-molecular weight glycoprotein expressed on type 2 pneumonocytes that is a useful marker for the clinical diagnosis of interstitial lung diseases and the evaluation of disease activity [2]. It was reported that the sensitivity, specificity, and diagnostic accuracy for KL-6 were 93.9%, 96.3%, and 95.7%, respectively, for interstitial lung diseases [3].

Herein, we describe a patient who avoided progression to severe IP induced by Peg-IFN α2a and RBV therapy by regularly measuring serum levels of KL-6.

CASE REPORT

A 58-year-old Japanese woman was referred to our hospital by her primary care physician for treatment of HCV likely stemming from a blood transfusion 33 years prior during childbirth. Her serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had been consistently greater than 30 IU/L. Chronic hepatitis was histologically proven by liver tissue biopsy, which revealed scores for periportal bridging necrosis,

intralobular degeneration and focal necrosis, and fibrosis of 1 each and a portal inflammation score of 3, with 20% fatty deposition as assessed by the Knodell hepatitis activity index (HAI) classification [4]. Her single nucleotide polymorphism of interleukin 28B at rs8099917 [5, 6] was G/G. She neither smoked nor habitually consumed alcohol. No history of pulmonary disease, frequent respiratory infection, or autoimmune disease was noted.

The patient was started on combination treatment of regular doses of Peg-IFN α2a 180μg s.c. once weekly and RBV 600 mg/day p.o. (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan). Serum HCV RNA was decreased to an undetectable level by Taq-Man assay 20 weeks after the initiation of therapy (Figure 1). She showed occasional mild hematopenia, resulting in periodic dose reductions of RBV to 400 mg/day (Figure 1). Serum levels of KL-6 were 251 U/ml (normal range: 105 to 435) at treatment onset and were regularly measured once a month. KL-6 began to rise noticeably from 12 weeks and reached 540 U/ml after 33 weeks of therapy, at which time peripheral white blood cell count and serum levels of C reactive protein and lactate dehydrogenase were 1,690 /μl with neutrophils of 900 /μl, 0.03 mg/dl, and 249 IU/L (normal range: 114 to 220), respectively. Although clinical symptoms of dry cough, fever, and dyspnea were undetectable, fine crackles could be heard during auscultation of her back. A computed tomography (CT) revealed bilateral patchy ground glass opacities around the dorsal area of the lungs (Figure 2a). No evidence of congestive heart failure was demonstrated by cardiac ultrasonography. Peg-IFN and RBV treatment was immediately discontinued due to suspicions of complicating IP.

She was observed carefully without any further medication. Serum levels of KL-6 continued increasing until 4 weeks after cessation of therapy to 731 U/ml and then decreased gradually, but did not return to pretreatment levels at her final medical checkup 10 months after cessation of therapy. Accordingly, she was monitored by regular follow-up at our outpatient clinic for further symptoms of IP and ultimately avoided development of severe IP. Serum HCV RNA became detectable by Taq-Man assay 12 weeks after discontinuation of Peg-IFN and RBV therapy, but a CT taken at 22 weeks after halting combination treatment depicted that the patchy ground glass opacities had diminished slightly (Figure 2b). An abdominal CT taken two years prior to therapy depicted negligible reticular interstitial shadows at the base of the lungs (Figure 2c), indicating that the patient might have been complicated with mild chronic IP at treatment onset.

DISCUSSION

Many side effects of Peg-IFN and RBV therapy have been reported, such as hematologic disorders, flu-like symptoms, neuropsychiatric disturbances, opthalmologic disorders, glucose metabolism disruption, autoimmune disease exacerbation, sarcoidosis, dermatologic complications, hair loss, and thyroid dysfunction; almost all of which can be managed with supportive care. It was also reported that respiratory tract symptoms, including a nonproductive cough and shortness of breath, may occur, [7] and that the etiology of dyspnea and other respiratory symptoms is usually attributed to anemic severity. A total of 10 cases that were complicated with IP during combination therapy have been reported to date [8-17]. Among them, no relationships with regards to age, gender, or type of

Peg-IFN were apparent. In addition, IP arose at any stage of treatment or hepatic fibrosis, and was unrelated to present or former use of tobacco. Clinical symptoms included fever, cough, and dyspnea in almost all cases, although these are nonspecific as physical findings in patients with IP. However, crackles may be present despite the absence of abnormities in chest X-rays; clinicians are advised to auscult the base of the lungs along the posterior axillary line when diagnosing for IP, as crackles may be audible in this location at disease onset, as presented in this case.

The mechanism of IP related to Peg-IFN and RBV remains elusive, but is considered to be related to pathophysiological and immunomodulatory causes. One of the main contributing factors to IP is the direct toxicity of the HCV treatment to the lungs. Another possibility is indirect mechanisms acting via immunological pathways, such as T-cell abnormalities [18]. We also cannot exclude the involvement of HCV itself in the pathogenesis of IP induced by interferon therapy since no such reports have been found for patients treated for hepatitis B virus. IP associated with IFN monotherapy [19] or Peg-IFN monotherapy [8] has been reported to date. However, RBV monotherapy has never been reported as the cause of IP since it is always given in conjunction with IFN or Peg-IFN for treatment of HCV. Thus, Peg-IFN, and not RBV, seems to have been the primary cause of IP.

Interstitial pneumonia developing during HCV treatment requires prompt detection and immediate discontinuation of Peg-IFN and RBV therapy [8-17] due to a reported mortality rate of seven percent [17]. Notably, three cases treated with Peg-IFN and RBV died from associating IP despite being treated

with corticosteroids after immediate IFN discontinuation [10, 12, 15].

Serum KL-6 is a sensitive marker of disease activity in fibrosing lung disorders [2, 3]. It was reported that KL-6 levels gradually increased from pretreatment levels when retrospectively measured every 12 weeks during a 48-week treatment course in chronic hepatitis C patients treated with Peg-IFN and RBV therapy, [20] although no patients developed IP in the cohort. Nonetheless, changes in serum KL-6 may provide useful information to assess early suspicions of IP, especially if accompanied by other diagnostic findings such as clinical examination or CT. In this case, a progression to severe IP could be prevented by discontinuation of combination therapy through monthly monitoring of serum KL-6. Her continuously elevated serum KL-6 has necessitated regular follow-up, and may be related to the persistent pulmonary shadows in chest CT.

In conclusion, clinicians should bear IP in mind as a complication during Peg-IFN and RBV combination therapy. Measurement of serum KL-6 is advised to detect and avoid progression of IP at an early stage.

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Authors' disclosures of potential conflicts of interest

The authors indicated no potential conflicts of interest.

Table 1: Published cases of interstitial pneumonia complicating Peg-IFN and ribavirin combination therapy in English literature

Case	Age (yrs)	Gender	Genotype	Fibrosis	Tobacco	Type of Peg-IFN	Peg-IFN (μg/week)	Ribavirin (mg/day)	Onset (weeks)	Clinical symptoms	Therapies	Result
1 [8]	48	female	2b	F3	N.D.	α2a	N.D.	N.D. +A	6	fever, cough	discontinuation and steroids	resolved
2 [9]	72	male	N.D.	N.D.	N.D.	α2b	1.5/kg	800	16	dyspnea	discontinuation and steroids	resolved
3 [10]	49	male	N.D.	cirrhosis *	former	α2b	150	1,200	2	cough, dyspnea	discontinuation and steroids	death §
4 [11]	71	female	2 and 4	N.D.	never	α2a	180	800	6	cough, shortness of breath	discontinuation	resolved
5 [12]	51	male	1a	F3 ※	N.D.	α2b	100	1,200	5	fever, dry cough, dyspnea	discontinuation and steroids	death #
6 [13]	58	female	1b	F3 ※	never	α2b α2a	1.5/kg 180	1,000 1,000 +A	12 12	dyspnea dyspnea	discontinuation and inhalation steroids	resolved
7 [14]	47	female	2b	cirrhosis **	never	α2b	100	800	8	dry cough, dyspnea	discontinuation and steroids	resolved
8 [15]	43	female	1b	cirrhosis *	N.D.	α2b	120	800	48	dyspnea, cough, fever	discontinuation and steroids	death $
9 [16]	68	male	1b	N.P.	N.D.	α2a	100	800	36	exertional dyspnea	discontinuation and steroids	resolved
10 [17]	51	male	3	F2 ※	N.D.	α2b	150	800	4	dry cough	discontinuation and steroids	resolved
Our case	58	female	1b	F1	never	α2a	180	600	33	none	discontinuation	resolved

Abbreviations: N.D., not described; +A, Amantadine; N.P., not performed; *, clinically diagnosed without histopathology; ※, METAVIR score [21]; **, histologically demonstrated as probable cirrhosis; §, death from acute respiratory distress syndrome and multi organ failure; $, death from progressive hypoxemia induced by IP; $, death from acute cholestatic hepatitis

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Figure Legends

Figure 1. Clinical course of the present case. Figure shows the time course of white blood cell count (WBC), hemoglobin level (Hb), platelet count, serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), lactate dehydrogenase (LDH), serum level of KL-6, and serum HCV RNA by Taq-Man assay. Serum levels of C reactive protein have been under 0.03 mg/dl during the clinical course (not shown). Shaded areas indicate the dosages of pegylated interferon (Peg-IFN) α2a and ribavirin (RBV). KL-6 began to rise noticeably from 12 weeks and reached 540 U/ml (upper limit of normal range: 435) after 33 weeks of combination therapy. A computed tomography (CT) performed at 33 weeks revealed findings compatible with interstitial pneumonia (IP) (Figure 2a). Peg-IFN and RBV treatment was immediately discontinued. The patient avoided development of severe IP without additional therapy.

Figure 2. a) A computed tomography performed at 33 weeks of treatment with pegylated interferon (Peg-IFN) α 2a combined with ribavirin (RBV) shows bilateral ground glass opacities (black arrow) and reticular shadows (black circles) located in the peripheral and dorsal areas of the lungs. b) The shadows were diminished slightly 22 weeks after discontinuation of Peg-IFN and RBV therapy. c) The patient's prior pulmonary condition depicted in an abdominal CT taken two years prior to treatment showed negligible reticular interstitial shadows at the base of the lungs, indicating that the patient might have had mild underlying chronic IP.

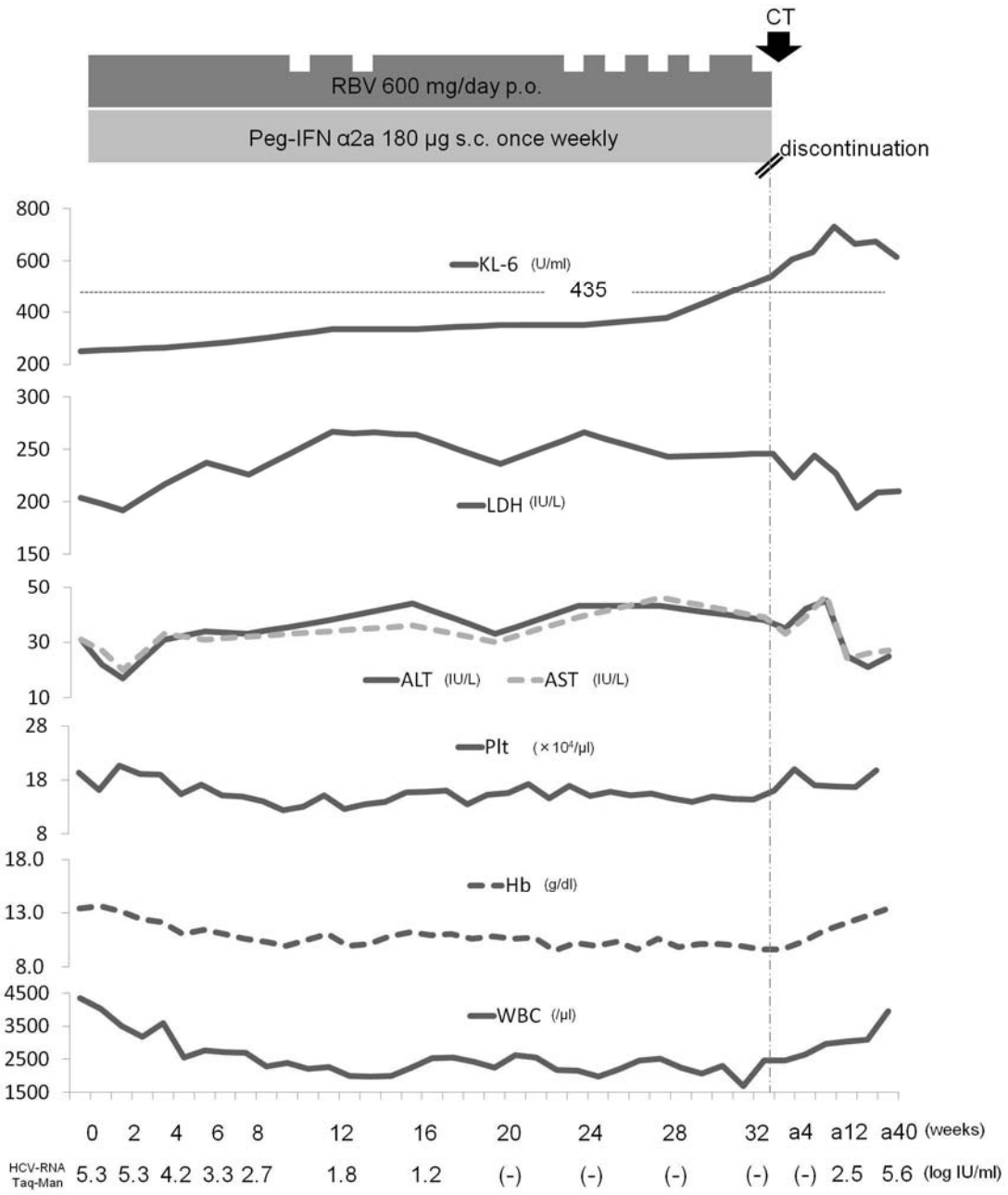
CT
RBV 600 mg/day p.o.
Peg-IFN α2a 180 μg s.c. once weekly
discontinuation
800
600
400
200
KL-6 (U/ml)
435
300
250
200
150
LDH (IU/L)
50
30
10
ALT (IU/L)
AST (IU/L)
28
18
8
Plt (×10⁴/μl)
18.0
13.0
8.0
Hb (g/dl)
4500
3500
2500
1500
WBC (/μl)
0 2 4 6 8 12 16 20 24 28 32 a4 a12 a40 (weeks)
HCV-RNA Taq-Man 5.3 5.3 4.2 3.3 2.7 1.8 1.2 (-) (-) (-) (-) (-) 2.5 5.6 (log IU/ml)

Figure 1

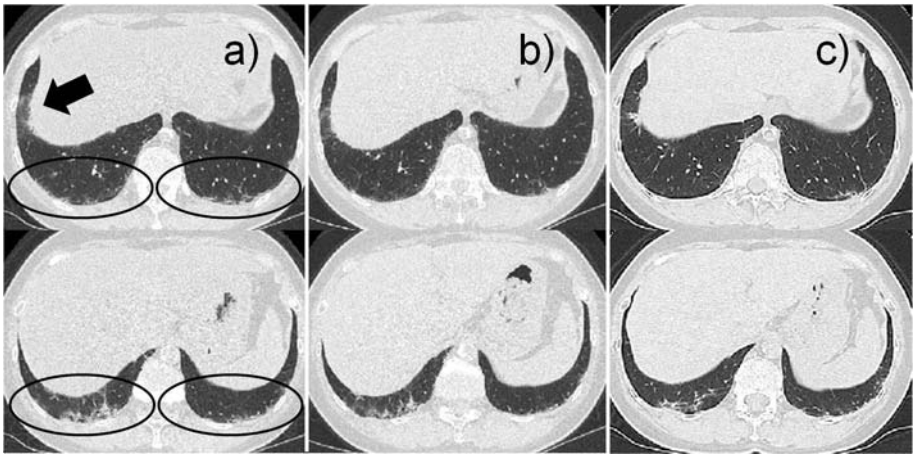

Figure 2