

CASE REPORT

## 만성C형간염을 동반한 만성 신부전 환자에서 인터페론 치료후 발생한 간질성 폐렴

강은정, 김동균, 전성란, 최현숙, 정승원, 장재영, 이준성, 어수택<sup>1</sup>

순천향대학교 의과대학 내과학교실 소화기연구소, 호흡기알레르기내과<sup>1</sup>

### Interstitial Pneumonitis in a Patient with Chronic Hepatitis C and Chronic Renal Failure on Interferon Therapy

Eun Jung Kang, Dong Kyun Kim, Seong Ran Jeon, Hyun Sook Choi, Soung Won Jeong, Jae Young Jang, Joon Seong Lee and Soo Taek Uh<sup>1</sup>

Institute for Digestive Research, Department of Internal Medicine, <sup>1</sup>Department of Allergy and Respiratory Medicine, Soonchunhyang University College of Medicine, Seoul, Korea

After 4-months of alpha interferon (IFN- $\alpha$ ), a 64-year old woman with chronic hepatitis C developed a cough and dyspnea and showed diffuse infiltrative opacities on her chest X-ray. Her symptoms persisted after stopping the IFN- $\alpha$  therapy. Pulmonary function testing revealed a reduced forced vital capacity. High-resolution computed tomography of the lung showed peripheral and peribronchovascular ground glass attenuation and consolidation associated with reticulation. Bronchoalveolar lavage was performed for further evaluation and showed a lymphocyte level of 8.2%, an uncommon finding in IFN- $\alpha$ -induced interstitial pneumonitis. We performed a lung biopsy to diagnose her disease and it suggested interstitial pneumonitis. This was considered to be due to the immunomodulatory effects of INF- $\alpha$ . Although rare, any sign of significant pulmonary involvement should be evaluated. (*Korean J Gastroenterol* 2011;58:47-52)

**Key Words:** Chronic hepatitis C, Interferon, Chronic renal failure, Interstitial pneumonitis

#### INTRODUCTION

Hepatitis C is caused by a small, single-stranded RNA virus which replicates in the liver at a high rate. The most common routes of HCV transmission are intravenous drug use, blood transfusion (before the advent of screening for the virus in the blood supply), and sexual exposure.<sup>1</sup>

Chronic infection (defined as detectable HCV RNA for more than 6 months) develops in 55-85% of patients with hepatitis C<sup>2</sup> and is a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma. Once established, chronic HCV in-

fection rarely resolves spontaneously.<sup>1</sup> Hepatocellular injury associated with chronic HCV disease appears to be mediated immunologically, with natural killer cells and CD8+ T-cells playing central roles.<sup>3,4</sup>

The recommended therapy for chronic hepatitis C is a combination of pegylated interferon alpha (IFN- $\alpha$ ) and ribavirin.<sup>5</sup> The attachment of polyethylene glycol (PEG) to interferon at the alpha site (peginterferon- $\alpha$ ) extends the half-life and duration of the therapeutic activity of INF- $\alpha$ . However, hepatitis C patients with renal failure are typically treated with reduced doses of peginterferon- $\alpha$  or conventional IFN. Additionally, rib-

Received December 4, 2009. Revised August 4, 2010. Accepted August 5, 2010.

© This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

교신저자: 장재영, 140-743, 서울시 용산구 대사관길 22, 순천향대학교 의과대학 내과학교실 소화기연구소

Correspondence to: Jae Young Jang, Institute for Digestive Research, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul Hospital, 657, Hannam-dong, Yongsan-gu, Seoul 140-743, Korea. Tel: +82-2-709-9863, Fax: +82-2-709-9696, E-mail: jyjang@hosp.sch.ac.kr

Financial support: None. Conflict of interest: None.

avirin is contraindicated in patients with renal failure because of its renal toxicity.<sup>6</sup>

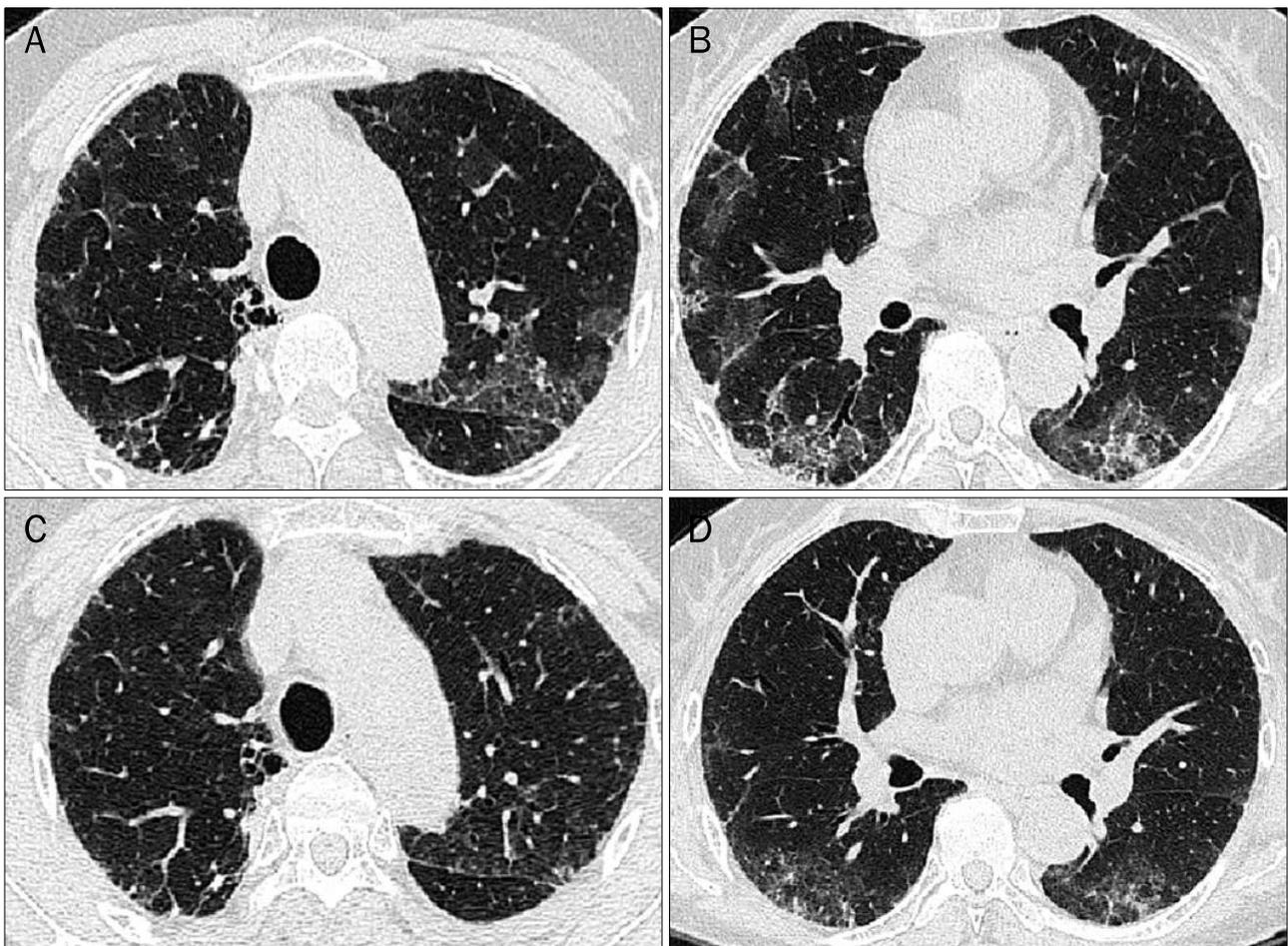
Interferon- $\alpha$  suppresses viral replication and restores elevated serum aminotransferase levels, leading to improvement in the histological changes in patients with chronic hepatitis C.<sup>7</sup> However, IFN- $\alpha$  can also induce various autoimmune disorders.<sup>8-10</sup> Here, we describe a patient with chronic hepatitis C and chronic renal failure who developed interstitial pneumonitis following IFN- $\alpha$  administration.

### CASE REPORT

The patient, a 64-year-old female, showed the first indications of abnormal liver function and tested positive for HCV antibodies in January 2006. Other than a history of chronic renal disease due to hypoplasia of the right kidney and renal artery stenosis, she had no history of autoimmune or

pulmonary disease. Dialysis was not performed. In April 2008, her ALT level was 68 U/L, her HCV RNA level (measured by PCR) was  $2.39 \times 10^4$  IU/mL, and her HCV genotype was 2a/2c. The liver parenchymal texture was coarse and both kidneys had decreased in size due to chronic renal disease: the right and left kidneys measured  $8.1 \times 3.0$  and  $6.9 \times 3.7$  cm, respectively. Following to the guidelines of The Korean Association for the Study of the Liver (KASL), the patient was started on 3-million units of IFN- $\alpha$  thrice weekly. After 4 weeks of therapy, she achieved a rapid virologic response (RVR).

However, the patient subsequently developed a cough, dyspnea, chills and myalgia, 4 months after starting IFN- $\alpha$  treatment. She had received a total of 54 million units of IFN- $\alpha$ . On admission, her white blood cell count (WBC) was  $3,400/\mu\text{L}$ , hemoglobin 9.3 g/dL, hematocrit 27.4%, and platelet count  $277,000/\mu\text{L}$ . Liver function tests were as follows: AST, 41 IU/L; ALT, 17 IU/L; LDH, 403 IU/L; ALP, 99 U/L; total

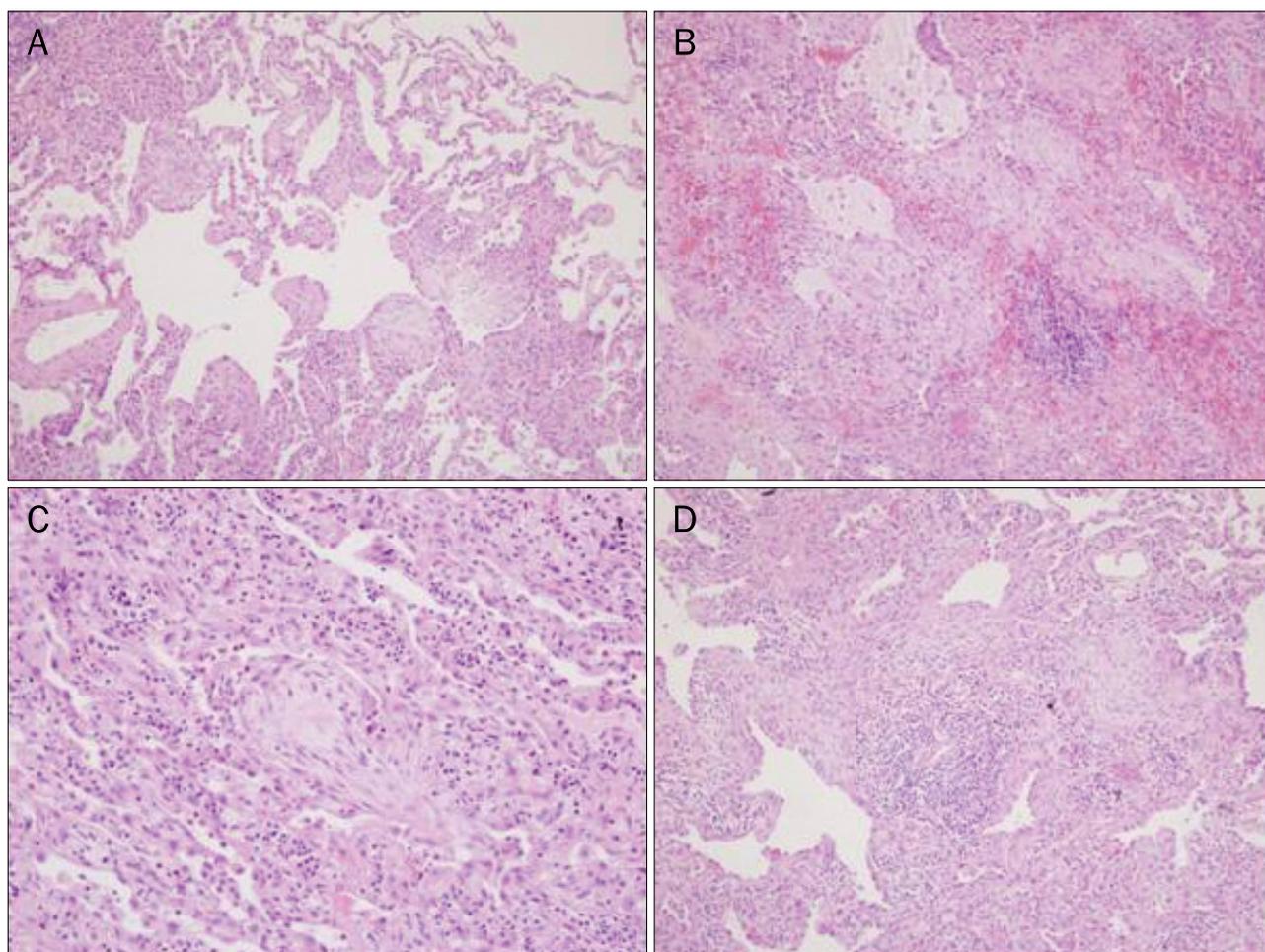


**Fig. 1.** (A, B) CT on admission showing peripheral and peribronchovascular ground glass attenuation and consolidations. (C, D) Repeated CT scan performed after discontinuation of interferon. Bilateral lung parenchymal lesions show improvement.

bilirubin, 0.3 mg/dL. The chest X-ray showed diffuse infiltrative opacities in both lungs. High-resolution computed tomography (HRCT) of the lung showed peripheral and peribronchovascular ground glass attenuation and consolidation associated with reticulation (Fig. 1A, B). Pulmonary function tests revealed a reduced forced vital capacity (Table 1-No.1). IFN- $\alpha$  induced interstitial pneumonitis was suspected and the IFN- $\alpha$  therapy was discontinued. Bronchoalveolar lavage (BAL) was performed for further evaluation and showed a lymphocyte level of 8.2%, an uncommon finding in IFN- $\alpha$  induced interstitial pneumonitis. Because there was no clinical improvement after halting the IFN- $\alpha$  and the BAL findings were atypical for IFN- $\alpha$  induced interstitial pneumonitis, a wedge resection of the lesion in the right lower lung was performed via video-assisted thoracoscopy. On microscopic examination, the lung showed patchy areas of organizing pneumonia

with polypoid plugs of loose connective tissue (Fig. 2A-C) and a chronic interstitial pneumonia pattern with interstitial thickening due to interstitial fibrosis and inflammation (Fig. 2D). There were also focal areas of emphysematous change, bronchiolization, and pleural thickening.

Three weeks after discontinuing the IFN- $\alpha$  therapy, follow-up HRCT showed improvement of the bilateral lung parenchymal lesions (Fig. 1C, D). Although pulmonary function tests showed slight improvement in the FVC (Table 1-No.2), the patient's dry cough persisted. Prednisolone was started at a dose of 25 mg daily, and her symptoms improved after 1 week. Over a 1-month period, the prednisolone was tapered to a dose of 7.5 mg daily. At last follow-up the patient's FVC had improved markedly (Table 1-No.3). Although she initially showed a RVR to INF- $\alpha$ , the patient's viral load increased again to  $2.43 \times 10^7$  IU/mL within 2 months of halting the INF- $\alpha$  therapy.



**Fig. 2.** (A) Patchy areas of organizing pneumonia showing polypoid plugs of loose connective tissue (H&E,  $\times 40$ ). (B) Polypoid plugs of organizing pneumonia and acute alveolar hemorrhage (H&E,  $\times 40$ ). (C) An organizing intraluminal plug with chronic inflammatory infiltrate (H&E,  $\times 100$ ). (D) Chronic interstitial pneumonia pattern with interstitial fibrosis and inflammation (H&E,  $\times 40$ ).

**Table 1.** The Cases of Interferon-induced Pulmonary Complications

No.	FEV1 (L) (% Predicted)	FVC (L) (% Predicted)	FEV1/FVC (% Predicted)	DLCO (ML/min/mmHg) (% Predicted)
1: On admission	93	75	88	45
2: After 1 mo	100	85	84	46
3: After 2 mo	110	95	83	58

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, carbon monoxide diffusing capacity.

Subsequently, we have monitored the patient's liver function and viral load without IFN- $\alpha$  treatment. Five months after ceasing treatment, the AST and ALT levels returned to near normal levels.

## DISCUSSION

The currently recommended regimen for the treatment of chronic hepatitis C is a combination of weekly subcutaneous peginterferon and twice daily oral ribavirin. In chronic hepatitis C patients with renal failure, according to the KASL guidelines, low-dose peginterferon or conventional interferon is indicated instead of peginterferon.

Currently, IFN- $\alpha$  is prescribed for many viral and neoplastic diseases, such as chronic hepatitis B and C, chronic myelogenous leukemia, hairy cell leukemia, multiple myeloma, and non-Hodgkin's lymphoma.<sup>11</sup> Common acute side effects of interferon treatment include fever, chills, weight loss and myalgia, which are typically transient. More serious conditions associated with IFN- $\alpha$  treatment include hemolytic anemia, interstitial pneumonia, cholestatic liver dysfunction, immune thrombocytopenia, and autoimmune thyroid disease.<sup>12</sup>

In 2002, Kumar et al. reported significant pulmonary toxicity associated with interferon and ribavirin therapy in four hepatitis C patients.<sup>13</sup> In four cases, lung biopsies revealed bronchiolitis obliterans organizing pneumonia (BOOP) in two cases, and interstitial pneumonitis in two cases.

The pathogenesis of autoantibody formation in IFN-induced autoimmunity is incompletely understood. A number of factors may alter the balance between self-tolerance and the activation of autoreactivity. IFN- $\alpha$  increases the activity of natural killer cells and cytotoxic T lymphocytes, and it enhances the expression of HLA class I and II antigens.<sup>10,14</sup> The increased expression of HLA-DR and CD 11b antigens in peripheral blood lymphocytes may indicate the activation of T lymphocytes and natural killer cells; furthermore, the increased

number of CD 8<sup>+</sup> T-cells in BAL fluid also suggests that cytotoxic T-cells in the lung were activated.<sup>10,12,14</sup> Thus in this case, interstitial pneumonitis response to IFN- $\alpha$  therapy was mediated immunologically. In interstitial pneumonia, IFN- $\alpha$  is considered an extrinsic antigen and potent immunomodulator and was responsible for the development and progression of IFN- $\alpha$  induced interstitial pneumonia.

Interferon toxicity is generally dose-dependent, increasing with the dose and duration of treatment. However, no clear relationship between the dose and likelihood of side effects has been demonstrated.<sup>15</sup>

Pulmonary complications due to interferon therapy for chronic hepatitis C typically occur within the first few weeks of therapy and can range from mild flu-like symptoms (e.g., fever, cough lasting more than 2 weeks while on therapy) to life-threatening hypoxemia and respiratory failure.<sup>16-18</sup> In our patient, a chest X-ray revealed bilateral diffuse reticulonodular infiltrates, pulmonary function tests showed a restrictive pattern, and the diffusion capacity was reduced. Based on these results, together with the mononuclear cell infiltrate on lung biopsy, a diagnosis of interstitial pneumonitis was made. A typical finding of IFN- $\alpha$  induced interstitial pneumonitis in BAL fluid is increased numbers of lymphocytes with elevated CD8<sup>+</sup>/CD4<sup>+</sup>. In this case, BAL showed a lymphocyte level of 8.2%, an uncommon finding in IFN- $\alpha$  induced interstitial pneumonitis. The lung biopsy showed patchy areas of organizing pneumonia and chronic interstitial pneumonia with interstitial thickening due to interstitial fibrosis and inflammation.

In most patients, IFN- $\alpha$  withdrawal or corticosteroid therapy alone is enough for spontaneous remission. However, persistent pneumonitis has been observed with high-dose corticosteroid therapy.<sup>19</sup> Most reported cases of interferon-associated pulmonary toxicity in patients with chronic hepatitis C were reversible; in many instances simply discontinuing the therapy or administering corticosteroids for a few months was

**Table 2.** Pulmonary Function Tests

	Gender	Age	Comorbidity	Type of IFN	Duration	PFT	Biopsy / BAL	Outcome
Kumar et al. <sup>13</sup>	Female	48	I.V. drug user	IFN- $\alpha$ 2b	24 wk	Reduced diffusing capacity	Bronchial mucosa	Resolved with steroids
	Male	50		PEG IFN- $\alpha$ 2a	6 wk	Restrictive pattern	Patch fibrosing interstitial pneumonitis	Mild exertional dyspnea persists after 1 yr on steroids
Chin et al. <sup>19</sup>	Female	58		Recombinant IFN	16 wk		BAL-Lymphocyte 74.2%, CD4/CD8 0.16	Resolved after the cessation of IFN treatment
	Female	72	Pulmonary emphysema	Natural IFN (Sumiferon)	10 days	Obstructive pattern		Maintain intermittent steroid pulse therapy
	Male	56	Taking herbal drugs	IFN (IntronA)	2 wk		BAL-Lymphocyte 38.7%, CD4/CD8 0.10	Resolved with steroid

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, carbon monoxide diffusing capacity; Aug, August; Sep, September; Oct, October.

sufficient. Kumar et al. reported two cases in which the symptoms resolved after simply discontinuing the antiviral therapy.<sup>13</sup> Another case improved after administering prednisolone. The final case showed persistent despite prednisolone treatment. We summarized these cases (Table 2).<sup>13,19</sup>

We experienced a rare case of interstitial pneumonitis secondary to interferon therapy in a 64-year-old female with chronic hepatitis C and chronic renal failure. Because no clinical improvement was apparent after ceasing IFN- $\alpha$  and BAL revealed an atypical finding in IFN- $\alpha$  induced interstitial pneumonitis, we confirmed the diagnosis of interstitial pneumonitis secondary to IFN- $\alpha$  with a lung biopsy. Three months after stopping the IFN- $\alpha$ , the patient's symptoms and liver function had improved (AST 41 IU/L; ALT 17 IU/L) and we stopped her prednisolone therapy.

This case illustrates potentially serious, but reversible, pulmonary toxicity associated with interferon therapy. Although rare, prompt investigation and discontinuation of medication is warranted if any sign of significant pulmonary involvement develops. We postulate that the usual dosage of interferon may have adverse effects in a patient diagnosed with chronic renal failure even without undergoing hemodialysis.

## REFERENCES

1. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med* 2006;355:2444-2451.
2. Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology* 2002;36(5 Suppl 1):S21-S29.
3. Rehermann B, Nascimbeni M. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat Rev Immunol* 2005;5:215-229.
4. Bowen DG, Walker CM. Adaptive immune responses in acute and chronic hepatitis C virus infection. *Nature* 2005;436:946-952.
5. Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004;39:1147-1171.
6. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001;345:41-52.
7. Davis GL, Balart LA, Schiff ER, et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. Hepatitis Interventional Therapy Group. *N Engl J Med* 1989;321:1501-1506.
8. Onoda K, Takai K, Sanada M, Aoki S, Watanabe T. Autoimmune hemolytic anemia induced by alpha-interferon therapy in a case of IgG-kappa type multiple myeloma. *Rinsho Ketsueki* 1992;33:844-846.
9. Schilling PJ, Kurzrock R, Kantarjian H, Gutterman JU, Talpaz M. Development of systemic lupus erythematosus after interferon therapy for chronic myelogenous leukemia. *Cancer* 1991;68:1536-1537.
10. Schattner A. Interferons and autoimmunity. *Am J Med Sci* 1988;295:532-544.
11. Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU. Clinical toxicity of interferons in cancer patients: a review. *J Clin Oncol* 1986;4:234-243.
12. Hizawa N, Kojima J, Kojima T, et al. A patient with chronic hepatitis C who simultaneously developed interstitial pneumonia, hemolytic anemia and cholestatic liver dysfunction after alpha-interferon administration. *Intern Med* 1994;33:337-341.
13. Kumar KS, Russo MW, Borczuk AC, et al. Significant pulmonary toxicity associated with interferon and ribavirin therapy for hep-

- atitis C. *Am J Gastroenterol* 2002;97:2432-2440.
14. Silva MO, Reddy KR, Jeffers LJ, Hill M, Schiff ER. Interferon-induced chronic active hepatitis? *Gastroenterology* 1991;101:840-842.
  15. Okanoue T, Sakamoto S, Itoh Y, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. *J Hepatol* 1996;25:283-291.
  16. Dumoulin FL, Leifeld L, Sauerbruch T, Spengler U. Autoimmunity induced by interferon-alpha therapy for chronic viral hepatitis. *Biomed Pharmacother* 1999;53:242-254.
  17. Wolf Y, Haddad R, Jossipov J, Werbin N. Alpha-interferon induced severe pneumonitis. *J Toxicol Clin Toxicol* 1997;35:113-114.
  18. Bini EJ, Weinshel EH. Severe exacerbation of asthma: a new side effect of interferon-alpha in patients with asthma and chronic hepatitis C. *Mayo Clin Proc* 1999;74:367-370.
  19. Chin K, Tabata C, Sataka N, Nagai S, Moriyasu F, Kuno K. Pneumonitis associated with natural and recombinant interferon alfa therapy for chronic hepatitis C. *Chest* 1994;105:939-941.