Pulmonary Abnormalities Caused by Interferon with or without Herbal Drug : CT and Radiographic Findings

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インターフェロンによる薬剤誘起性肺障害 —X線像およびCT像—

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インターフェロンによる薬剤誘起性肺障害の画像所見の特徴を知るために，C型肝炎に対してインターフェロン単独あるいはインターフェロンと漢方薬併用による治療中に急性びまん性肺障害を発症した5症例のX線像およびCT像を検討した．

X線像およびCT像の特徴は，スリガラス様陰影を伴うか，あるいは伴わない両側肺野に末梢優位に分布する肺胞性陰影を呈した症例が3例，両側中下肺野に微細網状影とスリガラス様陰影の混在した像を呈した症例が2例あった．インターフェロン誘起性肺障害の画像所見は単一ではないが，いずれもHypersensitivity reactionと考えられた．インターフェロンの使用頻度が高くなることが予想される今日，インターフェロン誘起性肺障害の画像所見について認識しておくことは極めて重要と考えられる．

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Introduction

Interferon is a cytokine, and it is widely recognized to be effective in use against some malignant diseases, including renal cell carcinoma, malignant melanoma, hairy cell leukemia[1),2)]. In 1989, interferon was proven to be effective for the treatment of chronic hepatitis C[3)–6)], and has been increasingly applied in recent years. Meanwhile, several side effects, such as autoimmune thyroiditis, heart failure, and acute renal failure, have been reported[7)–9)].

We recently experienced five cases with acute diffuse interstitial lung disease due to interferon administration, and this study serves to review the clinical features and chest radiographic and CT findings of these 5 cases.

Materials and Methods

The study group consisted of five patients with acute diffuse pulmonary disease which occurred in the course of interferon with (n=4) or without (n=1) a traditional herbal drug treatment for chronic hepatitis C.

All five patients had been diagnosed as chronic hepatitis C by means of immunological and histological examinations. They were treated with interferon alpha, whereby three to ten million units of interferon-α was injected every day for two weeks followed by repeated injection of the same dose every other day (Table 1). The duration of interferon treatment up to the time of respiratory illness ranged from one month to three months. The herbal drug was either sho-sai-koto or sairei-to which was popular Japanese traditional herbal medicine[10),11)].

Table 1 Pulmonary abnormalities caused by interferon with or without herbal drugs

Case	Age/Sex	Drug	Duration of IFN therapy	Symptoms	Means of diagnosis	Therapy
1	66/Male	IFN-α 2a Sho-saiko-to*	3 months	fever, cough, dyspnea	LST	Cessation of IFN, and sho-saiko-to, Corticosteroids
2#	59/Fmale	IFN-α 2b Sairei-to*	2.5 months	fever, cough, chest pain	TBLB, BAL LST	Cessation of IFN, and sairei-to
3	53/Female	IFN-α Sho-saiko-to*	1.5 month	dyspnea	TBLB, BAL LST	Cessation of IFN, and sho-saiko-to
4	63/Male	IFN-α 2b Sho-saiko-to*	1 month	fever, cough, dyspnea	TBLB, BAL LST	Cessation of IFN, and sho-saiko-to, Pulse therapy
5	61/Male	IFN-α 2b	1.5 month	fever, cough	Temporal sequence, LST	Cessation of IFN, Pulse therapy

Note. IFN=interferon, TBLB=transbronchial lung biopsy, BAL=bronchoalveolar lavage, LST=lymphocyte stimulating test, *Traditional herbal drugs. # Case 2 was previously reported[22].

Table 2 Radiographic and CT findings

Case	Radiographic findings	CT findings
1	Confluent consolidation Ground-glass opacities	Confluent consolidation (nonsegmental, air-bronchogram) Ground-glass opacties
2	Consolidation (inhomogeneous, mid-central)	Consolidation (band-like, nonsegmental) Linear or streaky shadow
3	Ground-glass opacities Patchy consolidation	Ground-glass opacities and air-space consolidation Streaky, or band-like opacities
4	Ground-glass opacities (diffuse) Consolidation	Ground-glass opacities Reticular lesion
5	Ground-glass opacities Reticulonodular lesion	Ground-glass opacities Reticular lesion

The respiratory symptoms consisted of cough (n=4), fever up (n=4), dyspnea (n=3), and chest pain (n=1) (Table 1). Hypoxemia was confirmed in all five patients (PaO2=49.2−70 mmHg). No specific risk factors or background conditions for pulmonary diseases were observed in these patients, and no other drugs than interferon or herbal drug which might cause pulmonary injury were used in these 5 patients.

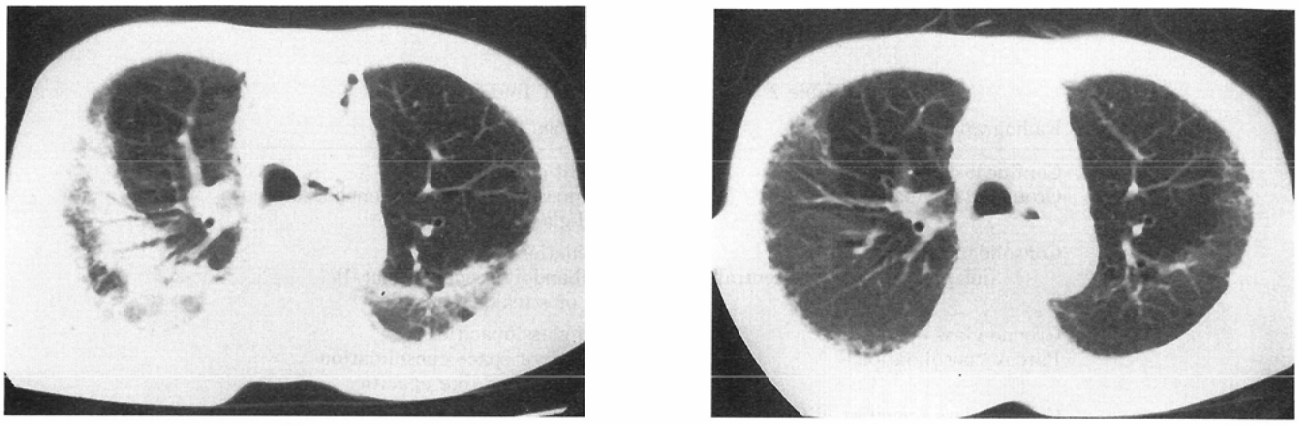
A diagnosis of interferon pulmonary toxicity was substantiated in all 5 patients by means of positive lymphocyte stimulating test for interferon-α using peripheral blood or bronchoalveolar lavage (BAL) fluid. Four patients who were treated with interferon and a herbal drug showed positive lymphocyte stimulating test for the combination of interferon and the herbal drug, while they showed negative lymphocyte stimulating test for the herbal drug itself. Transbronchial lung biopsy and bronchoalveolar lavage was performed in three of the 5, and BAL findings were compatible with drug-induced pulmonary injury; BAL fluid revealed an increased number of total cells and especially lymphocytes (n=3). Transbronchial lung biopsy findings were interstitial pneumonitis with mononuclear cell infiltration to alveolar septa (n=3). In one of the 3 cases, Masson body was also found within the alveolar space and respiratory bronchioles. Furthermore, in all 5 patients other infectious or hemodynamic causes could be clinically excluded. Improvement of radiographic and CT findings and clinical symptoms was obtained following cessation of the drug with (n=3) or without (n=2) administration of corticosteroids. Peripheral blood eosinophilia (eosinophilia 15.5 %) was noted in only one patient.

The CT scans, medical records, and conventional chest radiographs of these patients were reviewed. CT scans were obtained with a GE 9800 scanner (General Electrics, Milwaukee, USA) or a Toshiba 70A (Toshiba Co. Tokyo, Japan). Conventional CT scans with 10 mm-thickness and 1cm intervals were obtained in all 5 patients, and HRCT scans using bone algorithm with 1.5 mm-thickness and 2cm intervals were obtained in three patients.

The CT images and chest radiographs were independently reviewed by two observers paying special attention to the presence and distribution of airspace consolidation, ground-glass opacities, reticulation, interlobular septal thickening, honeycombing and other findings. When there was a discrepancy in the result, a decision was reached by consensus. On CT, ground-glass opacity was defined as an area of hazy increased attenuation without obscuration of underlying vascular markings. Consolidation was considered present when the vascular markings were obscured. Comparison between CT findings and radiographic findings was also performed.

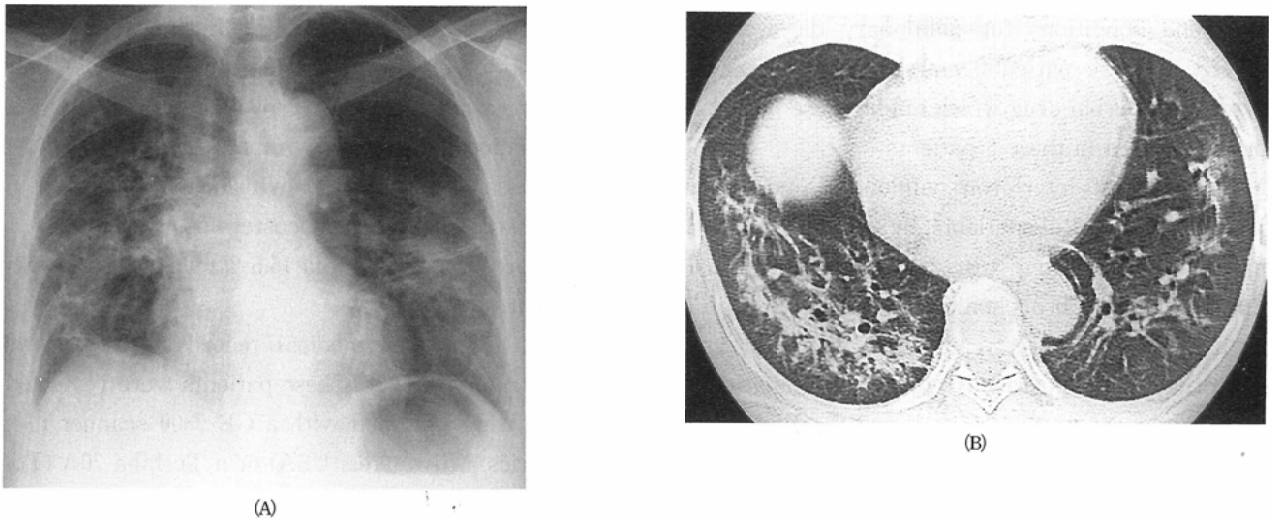
Results

Chest radiographic and CT findings were summarized in Table 2. On CT, widely disseminated ground-glass opacities were found in 4 of the 5 cases. Air-space consolidation was found in three. In all these three, air-space consolidation was non-segmental and the peripheral predominance of the consolidation was observed (Figs. 1, 2).One of the three had confluent consolida-



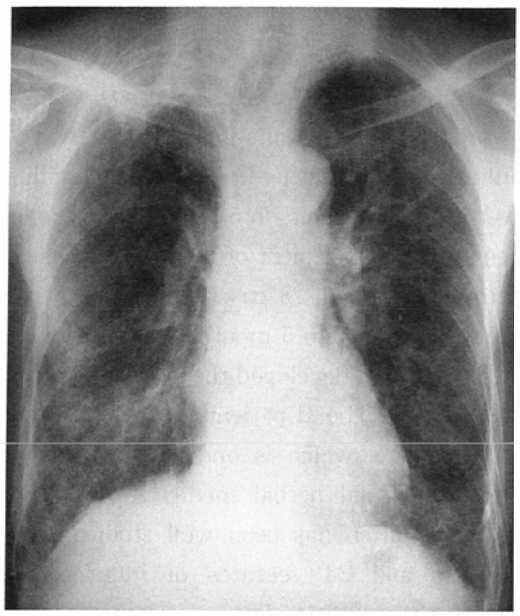
(A) (B)

Fig. 1 (Case No. 1) A 66-year-old woman with interferon-induced pulmonary diseases: The patient was treated with interferon-α 2a and sho-saiko-to for about three months. He complained of fever, cough, and dyspnea. Chest radiograph showed dense confluent consolidation, ground-glass opacities and reticulonodular shadow.
(A) Conventional CT scan at the A-P window level shows dense confluent consolidation with non-segmental distribution in both upper lungs. Air-bronchgram is clearly evident.
Seven weeks after cessation of interferon and sho-saiko-to, and administration of corticosteroid, the symptoms completely disappeared.
(B) Follow-up CT shows only ground-glass opacities.

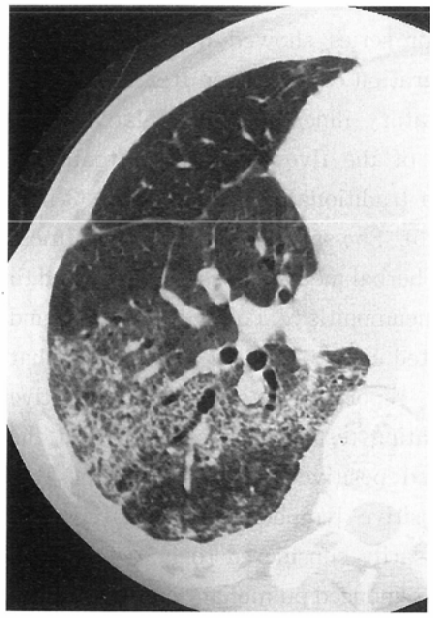


(A) (B)

Fig. 2 (Case No. 2) A 59-year-old woman with interferon-induced pneumonitis: The patient was treated with interferon-α 2b and sairei-to for two and a half month. Complaints comprised fever, cough, and chest pain.
(A) Chest radiograph reveals inhomogeneous consolidation. Peripheral predominance is not observed on chest radiograph.
(B) HRCT scan shows band-like nonsegmental consolidation, and linear or streaky shadows. Peripheral predominance is observed.



(A)



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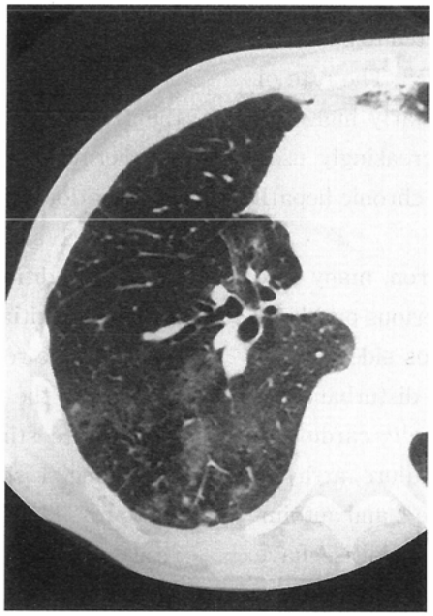
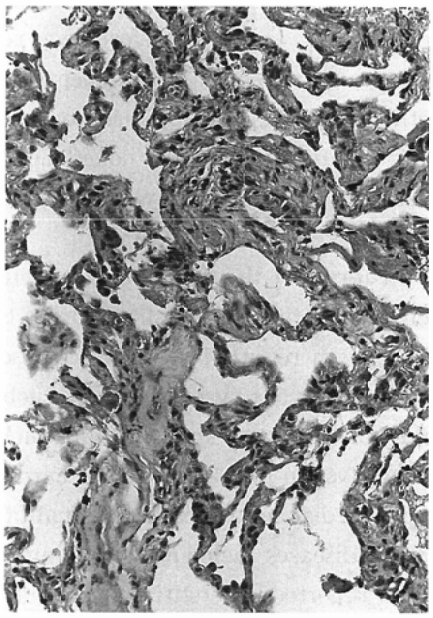


(C)



(D)

Fig. 3 (Case No. 4) A 63-year-old man with interferon-induced interstitial pneumonitis. The patient had a history involving a right upper lobectomy for pulmonary tuberculosis. He was treated with interferon-α 2b and sho-saiko-to for one month. Complaints were comprised of high fever, cough and dyspnea.

(A) Chest radiograph shows diffusely disseminated ground-glass opacities and patchy consolidation.

(B) HRCT scan at the level of the lower lung zone shows fine reticular shadow (intralobular reticulation), dense irregular opacity, and ground-glass opacities. Small branching structures and nodules are also observed.

Three weeks after cessation of interferon and sho-saiko-to, and administration of pulse therapy with corticosteroid, respiratory symptoms disappeared.

(C) HRCT scan after treatment shows only ground-glass opacities with patchy distribution.

(D) Transbronchial lung biopsy specimen from the right lower lobe reveals interstitial pneumonitis with mononuclear cell infiltration into the alveolar septa. Thickening of the alveolar wall and intraalveolar fibrosis are observed.

tion with air-bronchogram in contact with the pleura, and the other two were not in contact with the pleura, but showed band-like distribution parallel to the chest wall. Intralobular reticulation was observed in the ground-glass opacities in two other cases (Fig. 3). Intralobular reticulation was observed in the middle and lower lungs. Honeycombing, lung distortion or other findings were not found.

On chest radiography, airspace consolidation with or without groundglass opacities (n=4) and reticulonodular lesions with groundglass opacities (n=1) were observed. In one case (case No. 4), air-space consolidation and groundglass opacities were observed, while on CT air-space consolidation was not found, but intralobular reticulation was observed (Fig. 3). In the other case (case No. 2), band-like distribution of air-space consolidation and its peripheral predominance, which had been proved on CT, was not recognized on chest radiograph (Fig. 2).

Three patients were treated with corticosteroids while interferon administration was ceased. Two of the three underwent pulse therapy and the third received conventional corticosteroid treatment. In the remaining two patients, the treatment comprised cessation of interferon and a herbal drug only. Follow-up chest radiographs (n=5) and CT scans (n=3) after diagnosis were obtained, and the following results were observed. In

cases in which corticosteroid was employed,interferon-induced pulmonary abnormalities were almost resolved within a month. On the other hand, in the cases without corticosteroid therapy, it took one to two months to resolve interferon-induced pulmonary abnormalities.

Discussion

Interferon is one of the cytokines used as an anticancer cytokine. Interferon has been repeatedly employed against a number of malignant diseases including renal cell carcinoma, malignant melanoma, hairy cell leukemia, and chronic myeloid leukemia[1),2)]. However, the efficacy of interferon appeared somewhat limited, and recently a combined therapy with other anticancer drugs has been attempted against some malignancies, for example multiple myeloma and colorectal carcinoma[12),13)]. In 1989, interferon was reported to be useful for the treatment of chronic hepatitis C[3),4)]. The rate of efficacy of this therapy was not particularly high, but this treatment has been nonetheless increasingly used because no other effective drugs against chronic hepatitis C have been found[5),6)].

In terms of the side effects of interferon, many side effects ranging from a slight illness to serious problems have been reported[7)-9)]. As to the serious side effects, central nervous system damage such as disturbance of the consciousness and mental disturbance[14)], cardiovascular system problems such as cardiac failure, arrhythmia, cardiac infarction[8)], and renal failure[9)], and autoimmune diseases including autoimmune thyroiditis,[7)] have been reported. Interstitial pneumonitis was also reported as a rare complication[15),16)].

Recently, sporadic cases of interstitial pneumonitis, which occurring in the course of interferon treatment for chronic hepatitis C, have been reported. So far, thirty-one cases have been reported to the Pharmacological Affairs Bureau of the Japanese Ministry of Health and Welfare[17)]. A review of these 31 cases was performed in the "Side effect information of drugs" published by the same Pharmacological Affairs Bureau of the Japanese Ministry of Health and Welfare[17)]. Interstitial pneumonitis occurred between the ages of 40 and 70 years, with the highest incidence between the ages of 60 and 70 years (n=19), followed by in patients between 50 and 60 years (n=11). The patients comprised 13 males and 18 females. As to the subtypes of interferon, 8 were caused by interferon α, 16 were related to interferon α-2a, and the remaining 7 were linked to interferon α-2b. The cumulative dose of these drugs was found to be less than 100 million units in 6 cases, between 100 to 300 million units in 14, between 300 and 500 million in 6, and over 500 million units in 5 cases. As to the interval between the commencement of therapy and the onset of respiratory symptoms, 28 cases developed respiratory symptoms between 1 to 5 months after therapy began, and the other three developed the symptoms within one month. Twenty of the 31 patients were treated together with sho-saiko-to, which is one of the most popular Japanese traditional herbal medicines[10),11)]. Thus, the clinical information has been well studied, while the radiographic and CT features of interferon-induced pulmonary abnormalities have not been precisely described[17)].

Five cases in our series showed the same clinical situation in age, duration of interferon treatment up to the time of respiratory illness, and cumulative dose. Furthermore, four of the five cases were treated in combination with a traditional herbal medicine (3 sho-saiko-to, 1 sairei-to). Sho-saiko-to which is the most popular traditional herbal medicine has been reported to cause interstitial pneumonitis[18)]. Tomioka collected and analyzed the reported cases[18)], and he summarized that seven of the 11 reported cases showed positive lymphocyte stimulating test for sho-saiko-to, and the remaining 4 showed positive challange test for sho-saiko-to. Thus, positive lymphocyte stimulating test result is not necessarily considered to be a definitive proof of sho-saiko-to-induced pulmonary injury, but over 60 % of cases with this side effect show positive lymphocyte stimulating test results[18)]. In this situation, the most important question was which drug of either interferon or a herbal drug was responsible for diffuse pulmonary abnormalities in our cases. In our series, the diagnosis of interferon pulmonary toxicity was substantiated by positive lymphocyte stimulating test for interferon, not for herbal drugs. However, we don't know the reason why the incidence of this side effect of interferon becomes high when the herbal drug is used at the same time. Our five cases were collected from four different institutions, and we could not know the exact number of the patients in each institution who recieved interferon treatment for chronic hepatitis C. However, the number of the patients were roughly estimated as

over 200 cases.

The mechanism of this side effect of interferon with or without a herbal medicine has not been well understood, but some action related to the immune reaction may play an important role. The result of lymphocyte stimulating test, and BAL findings and the HRCT findings might support this speculation. Padley et al reported HRCT findings for drug-induced lung disease analyzing 23 patients with drug-induced lung damage, and classified the findings into four types corresponding to their pathologic observations. The four types comprised fibrosis with or without consolidation, ground-glass opacities, widespread bilateral consolidation, and bronchial wall thickening. The authors concluded that a hypersensitivity reaction was shown mainly as ground-glass opacities[19]. Cooper et al reported in a review of drug-induced pulmonary disease that nontoxic drugs might cause various types of reactions the same as cytotoxic drugs; (a) chronic pneumonitis/fibrosis, (b) hypersensitivity lung disease, (c) noncardiogenic pulmonary edema, (d) bronchiolitis obliterans, and (e) pulmonary renal syndrome. Radiographic findings of hypersensitivity lung disease were reported to be peripheral acinar infiltrates and diffuse reticular infiltrates[20),21)].

From the analysis of our cases, CT findings were peripherally predominant non-segmental consolidation (n=3) with or without groundglass opacities, or intralobular reticulation with groundglass (n=2). CT is more sensitive than radiograph in assessing the types and distribution of abnormalities, especially evaluating its peripheral predominance and non-segmental distribution. Furthermore, CT provides the information for guiding the site of transbronchial lung biopsy. Thus, CT is useful in diagnosing interferon-induced pulmonary injury when diffuse pulmonary disease is found in patients with chronic hepatitis C treated with interferon.

In conclusion, interferon-induced interstitial pneumonitis is a rare side effect, but its incidence is considered to be increasing due to the frequent use of interferon with or without a traditional herbal drug for the treatment of chronic hepatitis C. Radiologists as well as physicians must be aware of this side effect of interferon.

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