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Case report

Interstitial pneumonia induced by combined intraarterial 5-fluorouracil and subcutaneous interferon-α therapy for advanced hepatocellular carcinoma

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Previously we reported combined chemo-immunotherapy, using interferon (IFN)-α and 5-fluorouracil (5-FU) for patients with advanced hepatocellular carcinoma (HCC), and this regimen improved the prognosis. Recently, we experienced an HCC patient who died of severe interstitial pneumonia during the combined IFN-α and 5-FU therapy. This is the first report of the occurrence of interstitial pneumonia during combined IFN-α and 5-FU treatment. A 60-year-old-man was admitted to Osaka University Hospital to receive systemic chemo-immunotherapy for recurrent HCC. In the second week of the chemo-immunotherapy, he showed a decreased level of consciousness, and respiratory insufficiency. Emergency roentgenogram revealed diffuse infiltration in both lungs. Respiratory dysfunction due to interstitial pneumonia was suspected, and steroid pulse therapy was started. However, the patient showed respiratory failure, and he died 32 days after the start of the therapy. Autopsy findings showed atelectasis in the bilateral lungs, which showed elastic hard solidity and a dark red color; esophageal varices were also shown, and there was cirrhosis with a large tumor in the liver. Microscopically, the alveolar wall showed marked fibrous thickness and moderate inflammatory change, which is consistent with acute interstitial pneumonia, and the acute pulmonary change was suspected to have been the cause of death. The association of IFN with the development of interstitial pneumonia has been reported. However, the prognosis of IFN-induced interstitial pneumonia has mostly been favorable when the medication was discontinued. It has been postulated that interstitial pneumonia induced by the combination of IFN and 5-FU may be therapy-resistant. The combination of IFN-α and 5-FU is a useful therapy for patients with advanced HCC, such as that with portal vein invasion or multiple metastatic foci. Thus, interstitial pneumonia in these patients should be carefully managed.

Key words: hepatocellular carcinoma, interferon-α, 5-fluorouracil, interstitial pneumonia

Introduction

Interferons (IFNs) are cytokines with important functions in cell growth and regulation, and modulation of the immune system.[1] INF-α inhibits the proliferation of hepatoma cells and other neoplastic cells through the activation of natural killer cells.[2] Recently, we reported combined chemo-immunotherapy, using subcutaneous administration of IFN-α and intraarterial infusion of 5-fluorouracil (5-FU), for patients with unresectable hepatocellular carcinoma (HCC); the regimen improved the prognosis.[3,4] An association of IFN-α with the occurrence of interstitial pneumonia has been reported.[5] However, the prognosis of interstitial pneumonia induced by IFN-α alone is usually favorable when the medication is discontinued immediately.[6] However, the interstitial pneumonia induced by the combined use of INF-α and the Chinese herbal drug, "Sho-Sai Koto," a combination that had been frequently employed for the treatment of chronic hepatitis in Japan,[7,8] tended to be serious and therapy-resistant.

Recently, we experienced a patient with advanced HCC who died of interstitial pneumonia during the course of combined IFN-α and 5-FU therapy. This is an instructive case, with the patient having shown unusual pathologic manifestations of onion-like granuloma with

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interstitial fibrosis, resembling bronchiolitis obliterans organizing pneumonia (BOOP).

Case report

A 60-year-old man was admitted to Osaka University Hospital in July 2000 for the treatment of advanced HCC. He had been suffering from chronic hepatitis induced by hepatitis C virus (HCV) for 3 years. In June 1999, a tumor with a diameter of 3.5 cm had been found in the right lobe of the liver by ultrasonography. In July 1999, transarterial embolization (TAE) was performed, using Lipiodol (Mitsui Pharmaceutical Industry, Tokyo, Japan) and Gelform (Pharmacia & Upjohn, Peapack, NJ, USA), but this treatment was not effective because of poor accumulation of Lipiodol inside the tumor. A further TAE was done in March 2000, but this was also ineffective. During the follow-up period, multiple tumors were found in the liver, and the patient was referred to our hospital for systemic chemo-immunotherapy.

The laboratory data of the patient on admission were as follows: hemoglobin, 11.7 g/dl; leukocyte count, 7080/mm^3; aspartate aminotransferase, 76 IU/l; alanine aminotransferase, 46 IU/l; total bilirubin, 1.0 mg/dl; serum alpha-fetoprotein, 2890 ng/dl; serum carcinoembryonic antigen, 4 ng/ml; protein induced by vitamin K absence or antagonist-II, 54 000 mAU/ml; carbohydrate antigen 19-9, 112 U/ml; and HCV antibody, positive.

Computed tomographic scan showed a huge mass in the right lobe of the liver and multiple masses in the left lobe (Fig. 1). The right branch of the portal vein was occluded with tumor at the portion of the bifurcation. Angiography showed total occlusion of the main right branch of the portal vein and feeding from a branch of the superior mesenteric artery to the right lobe of the liver. Chest X-ray showed no abnormality at this time.

Clinical course

After we obtained informed consent from the patient, he was treated with subcutaneous administration of IFN-α (Otsuka Pharmaceutical, Tokyo, Japan) and intraarterial infusion of 5-FU (Kyowa Hakko, Tokyo, Japan). Five million units of IFN-α was administered on days 1, 3, and 5 of every week. 5-FU was infused continuously through the superior mesenteric artery, at a dose of 450 mg/day, every 2 weeks, via a catheter connected to a subcutaneously implanted drug delivery system. The second week of chemo-immunotherapy started on July 21, when the patient complained of loss of appetite. Catheterization of the subclavian vein was then performed for intravenous hyperalimentation. Chest X-ray showed slight infiltration in the upper right lobe. At the end of the second week of the therapy, the patient had a decreased level of consciousness and respiratory insufficiency that required oxygen mask support. Emergency chest X-ray revealed an increased area of diffuse infiltration in the right upper lobe, and new infiltration of all lobes of the left lung. He showed progressive dyspnea, and intubation with ventilation was done.

Chemotherapy was discontinued at this time. Laboratory data showed a high white blood cell count and a high level of C-reactive protein; sputum culture showed methicillin-sensitive *Staphylococcus aureus*, and antibiotic therapy was started for possible bacterial pneumonia or aspiration pneumonia. There was no significant improvement in his respiration after 1 week of antibiotic therapy, and tube tracheotomy was performed on

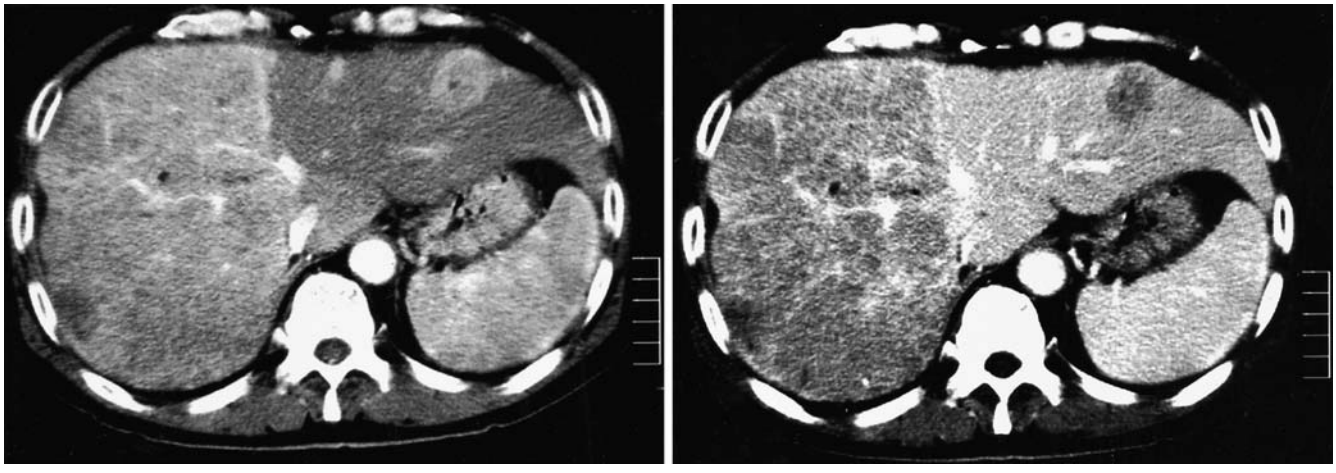

Fig. 1A,B. Computed tomography of the liver; multiple early-phase hyperattenuated (**A**) and late-phase isoattenuated tumors (**B**) were detected. The right lobe was replaced by tumor

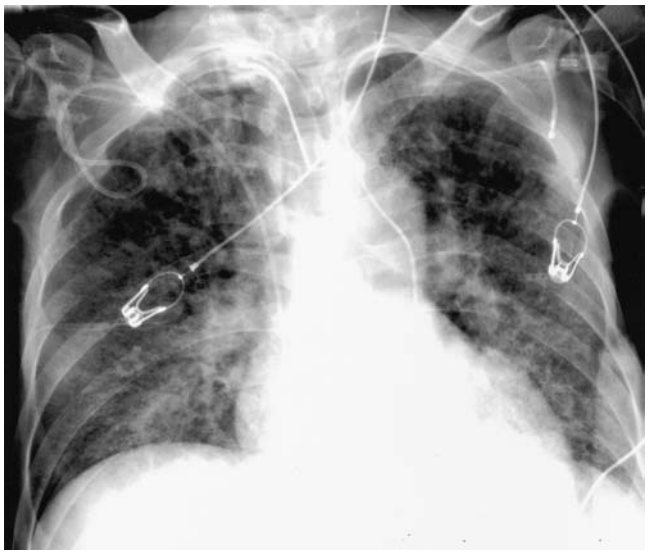

Fig. 2. Chest radiograph, performed on August 6, 24 days from the start of the chemo-immunotherapy, showed bilateral patchy infiltrations

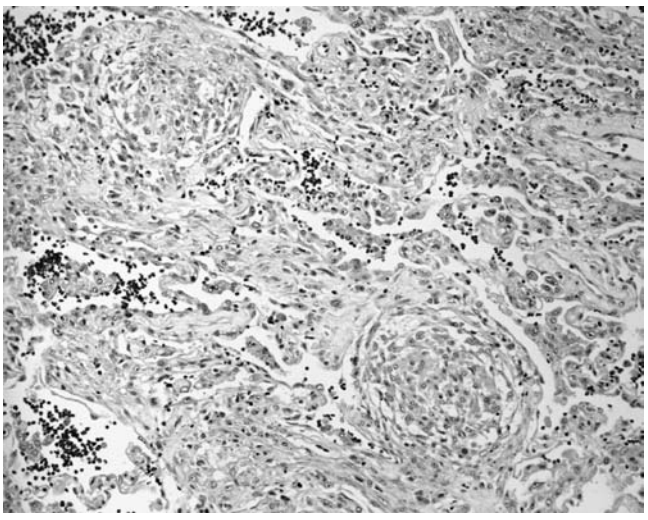

Fig. 3. Right upper lobe of lung autopsy specimen demonstrated marked fibrous thickness, with multiple well-formed granulomatous onion-skin-like lesions. H&E, ×100

August 6 (Fig. 2). The patient became febrile on August 7. Bronchoscopy and bronochoalveolar lavage (BAL) were performed on August 8, and showed the CD4/CD8 ratio in BAL fluid to be 1.62. Respiratory dysfunction due to interstitial pneumonia was suspected, and steroid pulse therapy was started on August 9. However, the patient did not recover from the respiratory failure, and he died on August 14. An autopsy was performed. The patient had not received the medication Sho-Sai Koto at any time throughout the course.

Autopsy findings

Macroscopically, both lungs showed atelectasis, with elastic hard solidity and dark-red color, and a white nodule, 1 cm in diameter, was seen in the lower lobe of the right lung. Multiple tumors, 1 to 4 cm in diameter, were seen in the left lung. Esophageal varices were observed. In the abdominal cavity, 800 ml of yellowish ascites was found. The liver was hard and cirrhotic, with an irregular surface and dull edge. The right lobe was totally replaced by an elastic, hard, white, tumor, 15 cm in diameter, which showed bleeding and massive necrosis.

Microscopically, the alveolar wall showed marked fibrous thickness, with multiple well-formed granulomatous onion-skin-like lesions (Fig. 3) and moderate inflammatory change. These findings were consistent with acute interstitial pneumonia, and we concluded that the changes in the pulmonary system were the reason for the respiratory failure and death of the patient. The tumors in the right lung were microscopic metastases of HCC. The liver showed cirrhosis with bridging fibrosis and piecemeal necrosis. The liver tumors were moderately differentiated HCC, trabecular type, with vascular invasion.

Discussion

IFNs are cytokines that have important functions in cell growth and regulation, and in the modulation of the immune system. IFN-α is increasingly used in the treatment of both malignant and nonmalignant diseases, such as myelofibrosis,[9] hepatitis C,[7] hairy cell leukemia,[10] cutaneous T-cell lymphoma,[11] myeloma,[10] and melanoma.[12] Experimentally, IFN-α inhibited the proliferation of hepatoma cells and other neoplastic cells by activating natural killer cells.[2]

The prognosis of advanced HCC is still unsatisfactory even with the current treatments.[13] Combined chemo-immunotherapy, using IFN-α and anticancer agents, could be a new therapeutic option for these patients.[4] We started using combination therapy of IFN-α and 5-FU for unresectable HCC and have reported an improved outcome with this therapeutic modality.

Interstitial pneumonia is induced through various pathways such as: (1) association with collagen vascular disease, (2) asbestosis, (3) hypersensitivity pneumonitis, (4) infection, (5) sarcoidosis, (6) drug-induced, and (7) unknown reasons (idiopathic interstitial pneumonia [IIP]). The "unknown reasons" category is further classified into the following four categories: (7-1) acute interstitial pneumonia/diffuse alveolar damage (AIP/DAD), (7-2) usual interstitial pneumonia (UIP), (7-3) bronchiolitis obliterans organizing pneumonia

(BOOP), and (7-4) nonspecific interstitial pneumofibrosis (NSIP).[14,15]

The present patient did not show any pulmonary symptoms before the combined treatment was started, and his chest X-ray on admission was normal. He did not have any history of medical disorders such as collagen disease or infectious disease. However, he developed dyspnea, fever, and diffuse pulmonary infiltrates shown on chest radiographs 2 weeks after the start of chemo-immunotherapy. This clinical history strongly suggests a causal relationship between the medication and the onset of interstitial pneumonia, although a precise relationship was not proved by the lymphocyte transformation test. The microscopic features of the lung showed interstitial fibrosis with thickening of alveolar walls, and granulomatous lesions in the parenchyma, features that are consistent with interstitial pneumonia.[15]

The association of IFNs with the development of interstitial pneumonia has been reported previously.[6,7] However, most patients with IFN-induced interstitial pneumonia reported in Japan were patients with hepatitis C who received combination therapy with IFN and Sho-Sai Koto, a Chinese herbal drug. It has been shown that Sho-Sai Koto itself was causative of interstitial pneumonia, and the combination therapy of IFNs and Sho-Sai Koto increased the risk for the development of interstitial pneumonia. Furthermore, the interstitial pneumonia induced by the combined use of Sho-Sai Koto and IFNs tended to be serious and therapy-resistant.[8] Therefore, combination therapy with these two drugs has been prohibited in Japan. As for 5-FU, there have been several reports describing the association of 5-FU with the development of interstitial pneumonia.[16] However, an increase in the risk of interstitial pneumonia by the combined use of IFNs and 5-Fu has not been reported.

The standard strategy for managing drug-induced interstitial pneumonia is to stop usage of the drug immediately, and then start steroid pulse therapy, combined with supportive therapy for severe respiratory conditions.[7] According to previous reports, the prognosis of IFN-induced interstitial pneumonia was mostly favorable if the medication was discontinued.[6,7] Our case patient developed acute respiratory failure, after which the medication was immediately withdrawn and steroid therapy was started, with mechanical ventilation support. The mechanism of interstitial pneumonia development induced by the combined use of IFNs and 5-FU is not yet clarified; however, it is supposed that the interstitial pneumonia induced by the combination of IFNs and 5-FU could be therapy-resistant and show a poor prognosis.[5] The duration between the start of the combined IFN and 5-FU therapy and the onset of interstitial pneumonia was very short in the present patient, compared to previous reports of interstitial pneumonia induced by either IFNs or 5-FU.[16–18] It is hypothesized that IFNs modulate the release of fibrogenic cytokines, such as platelet-derived growth factor and transforming growth factor-β; this modulation is relatively rapid and the effect is irreversible.[17] It is supposed that the combined use of IFNs and 5-FU may have accelerated the release of fibrogenic cytokines.

The present patient was at the end-stage of advanced HCC, with portal vein tumor thrombus and multiple intrahepatic metastatic lesions, and he may have had a much poorer reserve function than that in patients with chronic hepatitis receiving only IFN as antiviral therapy. Combination therapy of IFN-α and 5-FU is given to patients in poor general condition, such as those with portal vein invasion or multiple metastatic foci. Thus, interstitial pneumonia in these patients should be carefully managed.

In summary, we encountered a case of severe interstitial pneumonia induced by combined intraarterial 5-FU and subcutaneous IFN-α therapy for advanced HCC. As this therapy is used for high-risk patients with poor reserve condition, the occurrence of interstitial pneumonia in these patients should be carefully managed.

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