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. INF-α inhibits the proliferation of hepatoma cells and other neoplastic cells through the activation of natural killer cells. 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. An association of IFN-α with the occurrence of interstitial pneumonia has been reported. However, the prognosis of interstitial pneumonia induced by IFN-α alone is usually favorable when the medication is discontinued immediately. 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, 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/mm³; aspartate aminotransferase, 76 IU/l; alanine aminotransferase, 461 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, 54000 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.](image-url) 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