다발성 폐전이를 동반한 재발성 간세포암종의 자발퇴행 1예

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Spontaneous Regression of Recurred Hepatocellular Carcinoma with Multiple Lung Metastases

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Hepatocellular carcinoma (HCC) is the most common form of liver malignancy. Spontaneous regression of HCC is extremely rare phenomenon and mechanism of regression remains obscure. 75-year-old woman previously diagnosed with hepatitis C virus-related liver cirrhosis was found to have single mass in liver with elevation of α -fetoprotein level to 10,320 ng/mL. Transarterial chemoembolization (TACE) was performed. 27 months after TACE recurred HCC with multiple lung nodules were confirmed. The patient refused any therapeutic modality. The patient underwent follow-up without any anti-cancer treatment. 8 months after recurrence follow up computed tomography scan revealed spontaneous regression of HCC and completely disappeared lung nodules. The patient is currently doing well and without any evidence of recurrence. The causes of spontaneous regression of HCC are not well understood. Proposed mechanisms are ischemic injury, biological factors, herbal medicine, immunological variations. Further studies are necessary to improve our understanding of this rare phenomenon. (*Journal of Liver Cancer* 2015;15:46-51)

Keywords: Hepatocellular carcinoma; Lung metastasis; Spontaneous neoplasm regression; Therapeutic chemoembolization

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of liver malignancy and the fifth most common malignancy worldwide.¹ The prognosis remains poor for advanced HCC, which has an average length of survival of less than 6 months.² Patients with HCC commonly experience intrahepatic metastasis, with the lung as the most frequent organ for

distant metastasis.³ Spontaneous regression of malignancy is very rare, with an estimated incidence of 1 in 60,000 to 100,000 malignant cases.⁴ Spontaneous regression of HCC is an extremely rare phenomenon and the mechanism of regression remains obscure. Only approximately 50 cases have been reported to date.^{5,6} We report a case of a 75-year-old woman who showed spontaneous regression of multiple pulmonary metastases of HCC.

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CASE REPORT

A 75-year-old woman was followed up in the outpatient clinic for hepatitis C virus-related liver cirrhosis of 13 years

duration. She had a past medical history of blood transfusion during childbirth in 1968. She had no history of heavy alcohol intake. She had no serological markers for hepatitis B. In 1999, she was referred to our hepatology department with a diagnosis of hepatitis C virus-related liver cirrhosis. The pa-

tient was regularly followed up in our outpatient department with ultrasonography or computed tomography (CT) and examination of serum α -fetoprotein (AFP) level. The patient had not been taking any treatment for hepatitis or cirrhosis until 2010. In May 2010, CT revealed a liver tumor about 4

Figure 1. Abdominal computed tomographic findings of HCC. Contrast-enhanced abdominal computed tomography showed a 4 cm sized tumor in the liver. (A) The tumor was enhanced on arterial phase. (B) The tumor was washed out on delayed phase. HCC, hepatocellular carcinoma.

Figure 2. Abdominal computed tomographic findings 2 months after transarterial chemoembolization. (A) Abdominal computed tomographic findings after one session of TACE, no viable tumor were noted around lipiodol laden mass on arterial phase. (B) Abdominal computed tomographic findings after one session of TACE, delayed phase. TACE, transarterial chemoembolization.

cm in diameter that showed imaging features typical of HCC, and her serum AFP level was markedly elevated (10,320 ng/mL) (Fig. 1). She was clinically diagnosed with HCC and underwent transarterial chemoembolization (TACE) on June 2010. At the next follow-up (August 2010), no recurrent lesions were detected on CT and her serum AFP had dropped to 11.7 ng/mL (Fig. 2). Thereafter, the follow-up examinations, including CT and AFP, were performed every 3-6

months and showed no relapse of HCC. In September 2012, she complained of a dry cough. A chest X-ray showed numerous nodules in both lung fields and CT revealed a recurrent mass (about 6 × 6 cm) in the same region of the liver and multiple metastases in both lung fields, and her AFP level was elevated (472 ng/mL) (Fig. 3).

Based on the above findings, she was diagnosed with recurrent HCC with multiple lung metastases. We recommend-

Figure 3. CT and chest X-ray taken in September 2012 showing recurrent HCC and multiple nodular lesions in bilateral lungs, suggesting metastasis from HCC. (A) About 6 cm in size viable tumor around lipiodol laden mass were noted on abdominal computed tomography, delayed phase. (B) Multiple nodular lesions in bilateral lungs were noted on chest CT. (C) Multiple nodular lesions in bilateral lungs were noted on chest X-ray. CT, computed tomography; HCC, hepatocellular carcinoma, PA, posterior-anterior; LT, left.

ed that she undergo a second TACE. Because of her advanced age, the patient and her family refused any therapeutic modality for HCC and we decided on regular follow-ups. In February 2013, a follow-up CT scan and a chest X-ray revealed more aggravation of the primary lesion (up to 7 cm) of the liver and the pulmonary metastatic nodules. The patient underwent follow-up but received no therapy for HCC. Two months later (May 2013), a chest X-ray showed no pul-

monary nodules and a CT scan also revealed a decreased primary mass (about 3.7×3 cm), and her serum AFP had dropped to 22.7 ng/mL (Fig. 4). After a four month period of spontaneous regression, the patient is currently being followed up at an outpatient department and no imaging findings indicative of recurrent HCC or lung metastasis have been noted.

Figure 4. CT and chest X-ray taken in May 2013 showing marked reduction in size of recurrent HCC and no pulmonary nodule in bilateral lungs. (A) About 3.7 cm in size tumor around lipiodol laden mass were noted on abdominal computed tomography, delayed phase. (B) No pulmonary nodule in bilateral lungs on chest CT. (C) No pulmonary nodule in bilateral lungs on chest X-ray. CT, computed tomography; HCC, hepatocellular carcinoma.

DISCUSSION

Spontaneous regression was first defined by Chole and Everson in 1956 as the partial or complete disappearance of a malignant tumor without a specific therapy.⁷ The spontaneous regression of cancer is rare, with an incidence of one per 60,000-100,000 cancer patients.⁴ Spontaneous regression has been reported in a variety of malignant cancers, including HCC, but this phenomenon is more frequently reported in neuroblastoma, malignant melanoma, and cancer of the kidney.^{4,8-11} Various mechanisms have been proposed to explain spontaneous regression of HCC, with the most common being ischemic injury.^{5,9} Biological factors, herbal medicines, immunological variations, high fever, reduction of nutrients necessary for tumor growth, blood transfusion, surgical trauma, vascular injury, cytokines, and endocrine factors have also been suggested to explain spontaneous regression,^{6,9-13} but none of the proposed mechanisms satisfactorily explain spontaneous regression of HCC.

In our case, the underlying mechanisms leading to spontaneous regression are unknown because this patient received no medication, including herbal medicine, and no events or changes were evident. One mechanism that might be considered for this patient with rapidly growing tumors is that the interior of the tumor was relatively ischemic and this condition could have reduced the tumor size. However, this patient had a single tumor of the liver as well as nodules of various sizes in the lungs and all of these decreased in size at the same time. This observation was difficult to explain as being caused by an ischemia mechanism. An immune system mechanism has also been proposed as a cause of regression.¹⁴ One report indicated that an increase in cytokines such as interleukin-18 or tumor necrosis factor-alpha (TNF- α) was associated with spontaneous regression, but this was not verified in the present case.¹⁵

Malignant degeneration is a very rare natural phenomenon; therefore, it was important to distinguish whether the missing mass was a malignant or benign tumor. In the present case, it was necessary to distinguish whether the multiple pulmonary nodules were metastatic tumors, collagen vascular disease, or granulomatous inflammatory

disease. The recurrent liver tumor was not histologically confirmed as HCC. However, this patient had liver cirrhosis caused by chronic hepatitis C, the size of the tumor was 4 cm, and it showed a typical imaging pattern of HCC in CT with contrast enhancement in the arterial phase and the wash-out in the delayed phase. In addition, her AFP was increased to 10,320 ng/mL. Therefore, the patient met the criteria for diagnosis of HCC without a biopsy, according to the hepatocellular carcinoma diagnostic guidelines of American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL), and the Korean Association for the Study of the Liver (KASL). Multiple pulmonary nodules also occurred in this case of intrahepatic recurrence of HCC.

The CT findings indicated tumor metastasis and the increase or decrease in the size and number of pulmonary nodules was proportional to the serum AFP levels; therefore, it was considered advisable to view these as multiple pulmonary metastases of the HCC rather than as benign tumors. The exact mechanism that led to the natural destruction of HCC in this case is not known. The greatest difficulty in this study is the rarity of cases of spontaneous regression of malignant tumors. Accumulation of data from these cases in the future should lead to more research that can uncover the mechanisms and determine the nature of the regression of HCC.

In conclusion, we report a rare case of spontaneous regression of HCC with multiple lung metastases. None of the proposed mechanisms for spontaneous regression of HCC satisfactorily explains this regression. Further studies are needed to improve our understanding of this unusual event.

중심 단어: 간세포암; 폐전이; 자발퇴행; 화학색전술

Conflicts of Interest

The authors have no conflicts to disclose.

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