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Case report

Spontaneous regression of lung metastases after transarterial chemoembolization for hepatocellular carcinoma

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ABSTRACT

Spontaneous regressions of primary and/or metastatic lesions have been rarely reported in hepatocellular carcinoma (HCC). Herein, we report the case of a 71-year-old man with HCC, focusing on shape changes of lung metastases over time. Lung metastasis of HCC was histologically diagnosed by percutaneous computed tomography (CT)-guided needle biopsy after the treatment of primary HCC lesion. Lung lesions had been observed on enhanced contrast computed tomography for >3 years without any local or systemic treatment for them. During this period, treatments including surgical procedure for relapsed bladder cancer and transarterial chemoembolization for HCC were performed. Metastatic lung lesions immediately regressed after these treatments. Therefore, accumulation of such cases may help elucidate spontaneous regression mechanisms in primary HCC or its lung metastases.

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Introduction

Cancer cells are primarily characterized by their autonomous and indefinite growth. However, spontaneous cancer regression has been sporadically described in various cancer types and defined as partial or complete disappearance of a malignant tumor without specific treatments [1]. Spontaneous

regression of hepatocellular carcinoma (HCC) has also been reported [2-5], though extremely uncommon and reported as 0.1%-0.4% [3,6]. Several reports [7-10] described that spontaneous regression of lung metastases of HCC. However, no well-organized report has described a detailed clinical course and long-term outcome of lung metastases and primary lesions after the local treatment.

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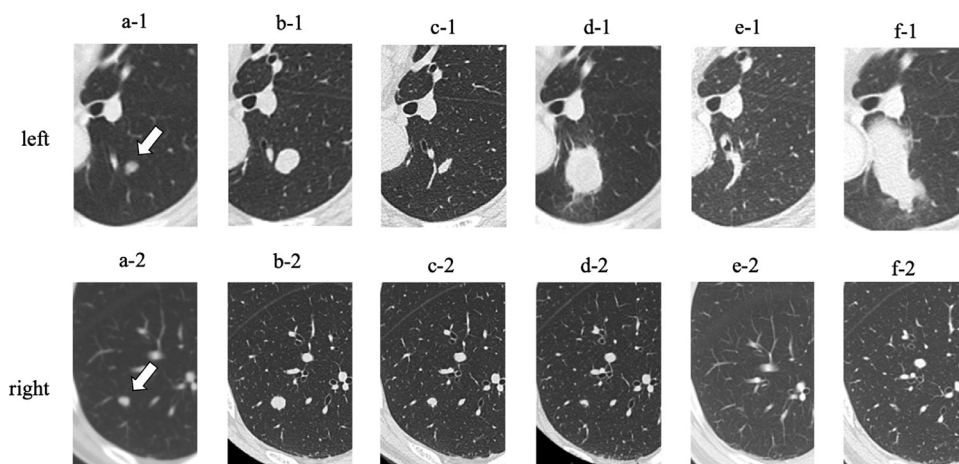


Fig. 1 – Chest CT images. The changes of CT images after referral our hospital are shown; 0 month (A), 4 months (B), 11 months (C), 17 months (D), 26 months (E), 35 months (F). The upper row shows left lower lobe (A-1 to F-1) and the lower row shows right lower lobe (A-2 to F-2). The arrows indicate the respective lesions. The shape and the size of 2 lung lesions on CT had been changed within 3 years. The maximum diameter: 11mm, 18 mm, 10 mm, 26 mm, none, 43 mm (Fig. A-1, B-1, C-1, D-1, E-1, F-1, respectively), 8 mm, 12mm, 8mm, 8mm, none, none (Fig. A-2, B-2, C-2, D-2, E-2, F-2, respectively). In addition, the concentration (CT value [Hounsfield Unit: HU]) inside the nodule was relatively uniform.

We report a case of HCC, with lung metastatic lesions revealing repeated spontaneous regressions and progression during the observation period of >3 years. In this case, spontaneous regressions of lung metastases were observed immediately after a surgical procedure for relapsed bladder cancer and after a transarterial chemoembolization (TACE) with radiofrequency ablation (RFA) for recurrent HCC tumor. These therapeutic procedures, indirect to metastatic lesions, might have some role on the regression of lung metastases.

Case report

A 71-year-old man with history of bladder cancer and HCC was referred to our hospital for evaluation of a pulmonary nodule. Five years before presentation, the patient was diagnosed with bladder cancer and had a curative urologic surgical procedure. Four years previously, the patient was diagnosed with hepatitis B virus-based HCC and underwent TACE with RFA therapy treated by an interventional radiologist (T.Y. with 23 years of experiences in interventional radiology). The patient had no symptom and his Child–Pugh score was A. Chest computed tomography (CT) examinations revealed bilateral lung nodules (left S6, 11 mm; right S9, 8 mm), suggesting metastases (Fig. 1A). However, biopsy was not performed during this time due to the small nodule size. No recurrence findings of primary lesion occurred in the liver.

Four months after detecting the first 2 lung lesions, their diameters were found to be enlarged (Fig. 1B). As bladder cancer recurrence occurred after 5 months, transurethral resection of the bladder tumor (TUR-BT) and intra-vesical injection of pirarubicin (PINORUBIN; Micro-Biopharm Japan, Tokyo, Japan) as an anti-neoplastic agent to

inhibit topoisomerase II were conducted. Eleven months thereafter, both-sided tumors showed regression (Fig. 1C). However, after 17 months, only the left lung lesion was markedly enlarged again, whereas the size of the opposite lung remained small (Fig. 1D). As HCC recurred at the primary site 18 months later, TACE with RFA was performed again, resulting in good local control. After 26 months, the right pulmonary tumor almost disappeared and only a mucus plug-like findings in the left lung remained in the bronchus (Fig. 1E). During this observation period, TUR-BT, intravesical injection of pirarubicin for bladder cancer, and TACE with RFA for HCC were performed. No specific treatment for lung lesions was performed because the lesion size changed during these procedures.

At 35 months thereafter, the patient was readmitted to our hospital for hemoptysis. The left-sided lung mass was markedly enlarged again filling the trachea of the left B6 (Fig. 1F). The serum PIVKA-II level was elevated despite the absence of local HCC recurrence (Fig. 2). ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) CT showed a high degree of accumulation (SUV_{max} , 8.7–9.2) at the left lung lesion (Fig. 3A). Bronchoscopy revealed areas of cancerous invasion to the bronchial mucosa (Fig. 3B). CT-guided lung biopsy (Fig. 3C) performed by an interventional radiologist (T.Y. with 23 years of experiences in interventional radiology.) histologically confirmed the pulmonary mass as metastasis of moderately differentiated HCC (Fig. 4). As the liver lesion was well controlled at this point, intensity-modulated radiation therapy was performed for the lung lesion. At 3 months after the radiation therapy, hemoptysis and lung lesion almost disappeared and PIVKA-II markedly decreased. In addition, as an immunological examination, at 3 months after initiating TACE with RFA, percentages of CD16+ NK cells and CD16+ monocytes, assayed by flow cytometry, were extremely high (12.1% and 8.8%, respectively).

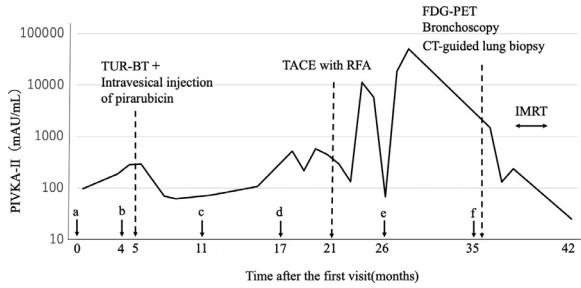


Fig. 2 – Clinical course. The line graph shows the trend of PIVKA-II. In this graph, a to f correspond to the timing of the chest CT scan, and the images correspond to A to F in Figure 1. The timing of examinations and treatments were also indicated in the graph. The lung lesions regressed after TUR-BT and TACE with RFA, respectively. PIVKA-II fluctuated in accordance with the size of the lung lesions. After 35 months from the first referral to our hospital, he had hemoptysis and the left lung lesion appeared again. The lung lesion was diagnosed as metastases of hepatocellular carcinoma by percutaneous CT-guided biopsy. After Intensity-modulated Radiation therapy, hemoptysis has been disappeared and PIVKA-II has normalized. PIVKA-II, protein induced by vitamin K absence/ antagonist-II; TUR-BT, trans-urethral resection of bladder tumor; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; FDG-PET, ^{18}F -fluorodeoxyglucose positron emission tomography CT; IMRT, Intensity-modulated Radiation therapy

The patient at the present age of 75 remains well without evidence of recurrence at 8 years after the HCC diagnosis and 4 years after the first detection of lung nodules.

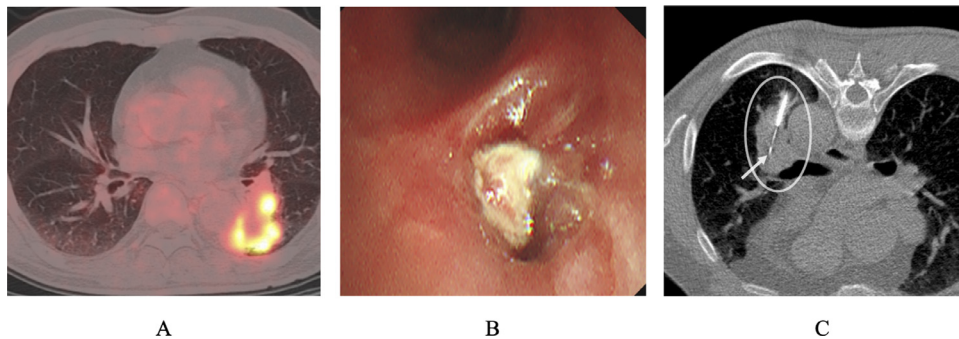


Fig. 3 – ^{18}F -fluorodeoxyglucose positron emission tomography CT, bronchoscopy image and CT-guided lung biopsy. Thirty-five months later, ^{18}F -fluorodeoxyglucose positron emission tomography CT showed a high degree of accumulation (SUV_{max} , 8.7-9.2) at the left lung lesion (A), and areas of suspected cancerous invasion to the bronchial mucosa was observed by bronchoscopy (B). Finally, CT-guided lung biopsy for the left mass was performed (C). A 18 G semi-automatic needle (MISSION, BARD Medical, Covington, GA, USA) was used to perform 2 biopsies in a prone position through the left back intercostal approach. The arrow indicates the tip of the biopsy needle, indicating that the biopsy needle has penetrated the left lung mass (circle).

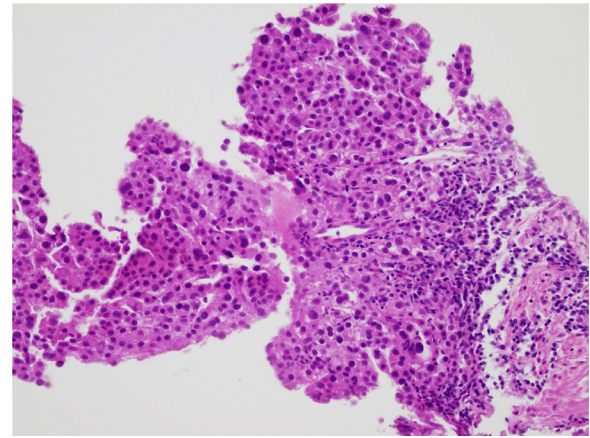


Fig. 4 – Histological findings. Hematoxylin-Eosin stain ($\times 200$) of the lung mass obtained by CT guided lung biopsy showed trabecular pattern with 4+ cells thick; tumor cells with centrality, round-like shaped nucleus and abundant granular eosinophilic cytoplasm; common pattern in moderately differentiated HCC.

Discussion

We described a unique case of HCC, with lung metastatic lesions revealing repeated spontaneous regression during the observation period of >3 years. Spontaneous regressions of lung metastases occurred immediately after TUR-BT, intravesical injection of pirarubicin, and after initiating TACE with RFA. The patient did not receive any other treatment such as systemic chemotherapy or radiation therapy for lung lesions during this period because they were difficult to diagnose using CT images due to lesion shape and size changes and using

bronchoscopy-guided biopsy probably due to an existence of necrotic or mucus component of the tumor. Therefore, these procedures for primary bladder and liver lesions might play some role on the regression of metastatic lesions at remote organs, but indirectly on metastatic lung lesions. In this case, the long-term observation of lung lesions revealed that observed regressions were not permanent and required radiation therapy at an appropriate timing after diagnosing metastasis from HCC by CT-guided needle biopsy.

Precise mechanisms of spontaneous HCC regression are still unknown; however, possible mechanisms have been suggested and categorized into 2 major types: tumor hypoxia and/or ischemia due to disruption of the feeding artery and systemic inflammatory or immunological reactions [4,5,11,12]. Other possible causes have also been sporadically described in HCC, such as vitamin K administration, herbal medicine, cessation of immunosuppressive therapy, prolonged fever, infection, massive gastrointestinal hemorrhage, abstinence from alcohol, or administration of megestrol, as described in review studies [4,11]; however, direct relationships of these factors and spontaneous regression are not yet clarified. Many cases were reported as truly spontaneous without any causative etiology [4,5,11].

Spontaneous regression mechanisms of metastatic lesions at remote organs have been discussed but remain to be clarified. Heianna et al. [8] reported spontaneous regression of lung metastases of HCC after TACE. They suggested that the release of antigen following HCC tumor lysis induced by TACE [13] may trigger host-immune activations such as cytokine activation [14], resulting in regression of metastases at remote organs. Our case did not receive any direct therapy for lung lesions, supporting that regression may be due to immune mechanisms triggered by TACE with RFA for the treatment of HCC from a viewpoint of the clinical course.

Arjunan et al. [6] recently reported that a patient with HCC showing spontaneous regression showed altered immunological subsets including extremely high CD16+ NK cell and CD16+ monocyte levels and strongly suggested host-immune participation for the tumor regression in HCC. At 3 months after TACE with RFA, percentages of CD16+ NK cells and CD16+ monocytes, assayed by flow cytometry, were extremely high in this case, which was consistent with their report [6]. Hence, involvement of host-immune participation may be relevant in such cases.

The present case showed that spontaneous regression, though transient, was also recognized postoperatively for relapsed bladder cancer. Therefore, the role of surgery on the regression of metastatic lung tumors remains unclear, and only a few reports have shown spontaneous regression in HCC after surgical procedures [15]. Prolonged inflammation or cytokine production postoperatively may be causative factors for the regression of metastatic lung tumors.

Another interesting point of this case is that the right lung tumor remained in regression, although the left lung tumor reappeared. Thus, the left lung tumor behavior was not associated with that of the right lung. One possible explanation is that some kinds of mutation change in left-sided lesions might have occurred to escape the immunological mechanism.

This case report has some limitations. First, the right lung nodule was not pathologically confirmed. Second, some parts of the left lung lesion might contain mucus plugs or blood components on CT images, except for the solid component of metastatic tumor; however, they were not confirmed by pathological findings.

In conclusion, spontaneous tumor regression is a clinically interesting phenomenon, although extremely rare. Since curative therapies are sometimes unavailable in patients with advanced cancer or those with distant metastases, accumulation and further discussion on spontaneous regression may have clinical implications for future cancer therapies and management.

Patient consent

Informed consent was obtained from the patients for publication of this report and accompanying images.

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