Lung metastases after liver cancer resection cured by immunotherapy: case report and literature review
Limin Ou, Guanhua Lu, Mingrong Cao, and Min Hu

The lung is the most common metastatic organ of primary liver cancer, accounting for 39.5–53.8% of extrahepatic metastasis, which seriously affects the prognosis of patients. In clinical treatment, it is difficult for one therapeutic schedule to achieve the desired effect sometimes, requiring two or even several combined methods for liver cancer lung metastasis. In this study, we report a liver cancer patient with lung metastases who received various combined therapies. However, the comprehensive treatment did not improve the patient’s pulmonary metastasis symptoms until after the application of immunotherapy, and the lung metastases were gradually cured. Anti-Cancer Drugs 34: e1–e8
Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: immunotherapy, liver cancer, lung metastases, the PD-1 inhibitor, case report

Background
Primary liver cancer (PLC) is the sixth most common cancer in the world. The poor prognosis of PLC makes it the second leading cause of cancer-related deaths worldwide (745,000 deaths account for 9.1% of total deaths) [1]. Extrahepatic metastasis is also one of the key factors affecting its prognosis and the most common sites of metastasis are the lungs [2,3]. Currently, potential therapies include hepatectomy, transhepatic arterial chemoembolization (TACE), hepatic artery infusion chemotherapy (HAIC), ablation, radiotherapy, molecular targeted therapy and immunotherapy. Although these treatments showed modest improvements in overall survival rates for early-stage diseases, the 3-year relative survival rate for distant metastasis patients remained low (3.1%) [4]. The prognosis of distant metastasis of liver cancer was extremely poor. The 1-year overall survival of patients with bone metastasis, distant lymphoid metastasis, lung metastasis and brain metastasis was 15%, 13.7%, 10% and 5.9%, respectively [5,6]. In recent years, with the continuous emergence of new therapeutic methods and the successful breakthrough of combined therapy exploration, the treatment of liver cancer has also undergone great changes. At present, the comprehensive treatment of advanced liver cancer has become one of the research hotspots. Through the scientific arrangement of local and systematic treatment, long-term tumor progression can be controlled and even clinical remission can be achieved. However, in many cases, comprehensive treatment is not effective for patients with distant metastasis of liver cancer. Therefore, new treatment methods need to be tried to achieve the purpose of curing distant metastasis of liver cancer. In this paper, a liver cancer patient with postoperative pulmonary metastasis was reported to have reached stabilization with immunotherapy.

Case presentation
A 45-year-old male patient was hospitalized with epigastric pain on 12 March 2018. The patient had suffered from chronic hepatitis B with positive e antigen for more than ten years and had not received formal treatment. Blood biochemical examinations on admission indicated slightly elevated liver function tests (Child-pugh A, ECOG-PS 1), while there was a significant elevation of alpha-fetoprotein (AFP) levels, 77,180.4 ng/ml (Fig. 1c). MRI of the upper abdomen in the other hospital suggested multiple lesions in the left lobe of the liver, considering primary hepatocellular carcinoma, with mild dilation of the common bile duct. Chest computed tomography showed fibroproliferative foci in the right-middle-lower lung and left pulmonary, accompanied by small nodules in the lower lobe of both lungs which regular review was recommended. Hepatobiliary ultrasonography in our hospital suggested an about 100 × 78 mm solid placeholder in the left liver, which was considered to be a high possibility of liver cancer. And this examination also reported a slightly stronger echo mass and striped blood flow signal in the main portal vein, suggesting portal thrombus (Fig. 2a). Chest X-ray showed double inferior pulmonary fibroproliferative foci and pleura thickening. Combining blood and imaging findings, the patient was diagnosed with liver cancer [China Liver Cancer Staging (CNLC) IIa, Barcelona Clinic Liver Cancer (BCLC) C]. The clinical
guidelines for PLC recommend that liver cancer resection is feasible for stage IIIa patients if the liver function Child-pugh A and ECOG-PS 1. According to the wishes of the patient and his family, the left hemihepatectomy and postoperative comprehensive treatment were chosen on 14 March 2018. Postoperative pathology revealed poorly differentiated hepatocellular carcinoma accompanied by vascular carcinoma thrombus (AJCC pT4N0M0, IIIB) (Fig. 3).

As shown in Fig. 1, 1 month after surgery, the liver function index returned to normal values and the AFP decreased to 8670 ng/ml. Hepatobiliary ultrasonography and upper abdomen MRI indicated no obvious abnormalities in the remnant liver, but there was portal vein tumor thrombosis (Fig. 2b). Multiple lung nodules were found on follow-up CT examination, which were considered metastatic tumors (Fig. 4a). Therefore, we believed that there was a possibility of pulmonary metastasis of liver cancer (CNLC IIIb) and developed a comprehensive treatment based on the above examinations and clinical practice guidelines. Subsequently, as Table 1 shows, the patient received 2 courses of HAIC based on FOLFOX every 3 weeks plus apatinib 0.25 g q.d. Whereas the lung metastasis tumor increased distinctly from the previous period (Fig. 5b) still accompanied by cough, and the AFP level rose from 8670 ng/ml in the early postoperative to 20979.16 ng/ml. Therefore, we believed that there was a possibility of pulmonary metastasis of liver cancer (CNLC IIIb) and developed a comprehensive treatment based on the above examinations and clinical practice guidelines. Subsequently, as Table 1 shows, the patient received 2 courses of HAIC based on FOLFOX every 3 weeks plus apatinib 0.25 g q.d. Whereas the lung metastasis tumor increased distinctly from the previous period (Fig. 5b) still accompanied by cough, and the AFP level rose from 8670 ng/ml in the early postoperative to 20979.16 ng/ml. Thereupon, the third and fourth HAIC and chemotherapy regimens were changed to oxaliplatin (L-OHP) combined with tegafur gimeracil oteracil potassium capsule (S-1) 60 mg bid every 3 weeks, and take apatinib 0.25 g q.d in the meantime, nonetheless, the tumor marker AFP level still elevated continuously to 158410.5 ng/ml 2 months.
Lung metastases cured by immunotherapy Ou et al. e3

later meanwhile cough symptoms continue to worsen. We changed the protocol again to percutaneous hepatic arteriography and bronchial artery perfusion chemotherapy combined with lobaplatin, epirubicine (EPI), fluorouracil (5-FU) and arsenic trioxide (As₂O₃), yet the AFP level remained 85100.6 ng/ml (Fig. 1c). Amazingly, two courses of immune checkpoint inhibitors (ICI) programmed cell death protein 1 (PD-1) inhibitors Opdivo followed at 1 September 2018, the patient’s general condition took a favorable turn and the level of AFP (86209.8 ng/ml), decreased compared to the previous level. The AFP level continuous declined after the 5 cycles of immunotherapy with domestic PD-1 inhibitors “Sintilimab” and remained low level (3.92 ng/ml). Moreover, imaging suggests that the number of chest metastatic tumors was significantly lower than before and the efficacy was evaluated as a partial response (Fig. 4; Fig. 5). Up to December 2021, the patient had no recurrence of the liver tumor and continued to shrink the lung metastases.

Discussion
Extrahepatic metastases usually occur during an advanced stage of the disease and offer a dismal prognosis [7]. The researchers believe that lung metastasis of liver cancer is related to the following mechanisms: the first mechanism is that hepatic veins was invaded by tumor, and tumor cells are carried to the pulmonary circulation through the intrahepatic portosystemic venous shunts or lymph draining from the main or right thoracic duct [8]. Second, the lungs provide a favorable environment for cancer cells due to the hypercoagulable state of blood and slow blood flow [9]. Third, extrathoracic malignancies systemically reprogram the lung microenvironment to support the colonization and outgrowth of disseminated tumor cells (DTCs) to generate secondary lung tumors [10]. The reprogramming mechanism includes increased cell adhesion, recruitment of neutrophils and macrophages, inhibition of cytotoxicity and maturation of NK cells, and thus the creation of immunosuppressive premetastatic niches [11].

The treatment of lung metastasis of hepatocellular carcinoma (HCC) mainly includes surgery, local ablation, radiotherapy, molecular targeted therapy and vascular interventional therapy. Surgery is generally applicable to patients with less than 3 intrapulmonary metastases that can be completely resected, but the complications are...
higher at 68.2% [12]. Lung ablation is suitable for a small number of lesions with a tumor size <3 cm. Some clinical studies showed that ablation had a 100% success rate for patients with liver cancer lung metastasis and a median survival of 28.7 months [13]. The overall response rate (ORR) of CT-guided radiotherapy was 80%, with a complete response rate of 24.7% and a partial response rate of 55.29%. External radiation therapy is used for patients with large lung metastases, malignant pleural effusion, atelectasis and tumor invasion of special sites [14]. Targeted drugs, systemic chemotherapy or a combination of targeted and immunologic drugs are recommended in the latest edition of the Health And Health Commission’s Guidelines for primary liver cancer diagnosis and treatment (2020 edition), for patients with advanced HCC in good condition. The ORR of first-line chemotherapy and targeted drugs for advanced hepatocellular carcinoma was only 8% and 7%, and progression-free survival (PFS) was 2.9 and 3.8 months [15–17], respectively, still insufficient to meet patients’ need for significantly prolonged survival.

In this case, the patient developed bilateral lung metastasis 1 month after hepatectomy. Fluctuations in liver function indicators such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB) and total bilirubin (TBIL) in patients are related to medication or surgical treatment (Fig. 1a,b), but the fluctuation of the index did not affect the patient’s liver function and the next course of treatment. As we can see in Fig. 1c, AFP continuous elevated in the first couple of combination sessions. After initiating immunotherapy in September 2018, AFP began to decline continuously and significantly. Despite chemotherapy and targeted...
therapy, the chest x-ray shows a keep growing in double lung metastases from 3 months postoperatively to 16 months (Fig. 5) and pulmonary symptoms worsen. The patient who attempted immunotherapy after the launch of immunodrugs experienced a significant reduction in bilateral pulmonary nodules by December 2021. Figure 2 shows the changes in hepatobiliary ultrasound before and after surgery. Preoperative portal vein ultrasound suggested slightly stronger echo clumps in the portal vein trunk, considered portal vein trunk carcinoma thrombosis. Nevertheless, 2 months after the operation, a hepatobiliary ultrasound indicated that portal vein blood circulation was unimpeded, which could be probably a function of the two courses of HAIC and TACE treatments. Previous studies have shown that there is an anatomical shunting of blood vessels in liver cancer. The blood supply of portal vein tumor thrombus (PVTT) in some HCC patients may primarily come from the hepatic artery [18,19], which makes PVTT respond well to transhepatic artery chemotherapy [20]. Some studies have demonstrated significant efficacy of HAIC in HCC patients with PVTT and have shown a survival benefit [21,22]. TACE combined with low-dose continuous hepatic arterial perfusion has also been shown to be effective and less toxic for HCC patients with PVTT [23]. Patients in our cases further provided evidence that transhepatic arterial chemotherapy therapy was effective for liver cancer with portal vein tumor thrombus. Figure 4 shows the changes in chest CT and maximum tumor volume in patients. As shown in Fig. 4b, the...
patient’s maximum tumor volume was larger than before. Combined with the decline in AFP, we believed that it is an inflammatory enlargement of the tumor because of the infiltration of inflammatory or immune cells due to the death of tumor cells. After a period of treatment, as shown in Fig. 4c, the volume and number of tumors decreased notably.

In recent years, immunotherapy has been considered one of the most effective methods for the comprehensive treatment of lung metastasis of HCC [24]. “Immunotherapy” is a general term that includes a wide range of applications and targets, including HCC vaccines, adoptive cell therapy (ACT), immune checkpoint inhibitors (ICI), and oncolytic viruses. In this case, what we used successfully

| Time      | Therapies                                                                 | Medicine                                                                 | Symptom                        |
|-----------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------|
| 2018.03.14| Liver cancer resection                                                    |                                                                          | Epigastric pain, cough         |
| 2018.04.19-05.19 | HAIC + chemotherapy                                  | FOLFOX: L-OHP 150 mg +CF 600 mg +5-FU 3.75g q3w +apatinib 0.25g q.d | Cough                          |
| 2018.06.12-07.02 | HAIC + chemotherapy                                  | L-OHP 150 mg +S-1 60 mg bid d1-14 +apatinib 0.25g q.d                      | Cough getting worse            |
| 2018.08.22 | Pericutaenous hepatic arteriography and bronchial artery perfusion chemotherapy | Lobaplatin 30 mg +EPI 20 mg +5-FU 1g +As2O3 20 mg                      | Cough                          |
| 2018.09.01-09.17 | Immunotherapy                                       | Opdivo                                                                  | Symptoms improved              |
| 2018.10.09-2021.12.13 | Immunotherapy                                       | Sintilimab                                                              | No discomfort                  |

CF, calcium folinate.

Fig. 5

Chest radiographs and changes in maximum tumor volume. (a) Preoperative chest x-ray: double foci of inferior pulmonary fibrosis; thickening of the right inferior pleura. (b) Three months after the surgery: multiple metastases in both lungs, the largest nodule was located in the lower lobe of the right lung, about 2.5 × 3.6 cm. (c) After 4 courses of chemotherapy and HAIC; the nodules in both lungs were increased and enlarged. The largest nodule was located in the lower lobe of the right lung, about 3.5 × 3.3 cm. (d) After 1 course of immunotherapy; the nodules in both lungs were increased and enlarged. The largest one is located in the lower lobe of the right lung, which was about 4.9 × 4.5 cm in size. (e) 45 months after surgery; the nodules in both lungs were significantly reduced, and the larger nodules were located in the lower lobe of the right lung with a size of about 3.2 × 3.5 cm.
Lung metastases cured by immunotherapy Ou et al.

was ICI. Metastatic distal organs enrich a large number of chemokines, which weaken the T cell-mediated anti-tumor immune response, and also promote the formation of physical barriers in tumor extracellular matrix and connective tissue to keep effector T cells out of the tumors. Programmed cell death-ligand 1 (PD-L1) is expressed on the surface of cancer cells and interacts with PD-1 on T cells to inhibit apoptosis of regulatory T cells and induce apoptosis of cytotoxic T cells. Immune checkpoint blockade therapy is designed to improve immune cell function or inhibit immunosuppressive activity [25]. ICI was used to suppress the immunosuppressive signalling network and restore T cell-mediated anti-tumor immunity. Several studies have shown that PD-1 monotherapy for advanced hepatocellular carcinoma patients has a relatively higher objective response rate and longer overall survival than chemotherapy and targeted drugs, showing good benefits [26,27]. An increasing number of clinical data suggests that tumor immunotherapy can provide patients with a lasting immune response and long-term survival benefits [28]. The patient, in this case, had a long-term stable status after treatment, and there was no significant progression in his condition, showing a sustained smearing effect of PD-1.

PD-1 monotherapy and dual immunotherapy have been approved for second-line treatment of advanced liver cancer. First-line targeted combination immunotherapy for advanced liver cancer made a tremendous breakthrough last year. Based on the IMbrave150 study, atezolizumab plus bevacizumab has been approved for the first-line treatment of liver cancer [29]. IMbrave150 is a global Phase III study of 501 patients with unresectable liver cancer who have not previously received systematic treatment. Patients were randomized to receive either atezolizumab plus bevacizumab or sorafenib according to the 2:1 ratio. Results showed that the ORR of the combination group was 27.3%, significantly higher than that of the sorafenib group (11.9%). In addition, combination therapy can also delay the deterioration of a patient’s quality of life [30]. Although the patient in our study did not receive targeted simultaneous combination immunotherapy since he was treated in 2018–2021, his curative effect was prominent and there were no obvious adverse reactions. Most importantly, his 3-years survival, for now, has been still a surprising statistic.

Conclusion

The treatment of primary liver cancer lung metastasis involves a variety of therapies and different specialities. It is necessary to strengthen the communication of relevant disciplines and seek the most effective comprehensive treatment mode, which is an important way to further improve the effectiveness of treatment. The immunotherapy model has attracted much attention and becomes a new therapeutic trend. With the development of research, more attention should be paid to how to formulate the optimal personalized comprehensive treatment plan, thus continuously improving the final results of clinical efficacy.

Acknowledgements

We gratefully acknowledge the participation of our patients.

This work was supported by the Natural Science Foundation of Guangdong Province-General Project [grant number 2214050003621]; the Jinan University Scientific Research Cultivation and Innovation Fund [Youth Fund Project: 11619356]; and the Flagship speciality construction project-General surgery [Funding number 711003].

All patients provided informed consent for the use of their data for research purposes. The study protocol was approved by the ethics committee of Jinan University First Affiliated Hospital.

LO and GL wrote this article; MH and MC supplied the study conception. All authors read and approved the manuscript.

The authors state that all data generated during this study are included in this published article.

Conflicts of interest

There are no conflicts of interest.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. (1542-4863 (Electronic)).
2 Uchino K, Tateishi R, Shina S, Kanda M, Masuzaki R, Kondo Y, et al. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. (1097-0142 (Electronic)).
3 Natsuzaka M, Omura T, Akaite K, Kuwata Y, Yamazaki K, Sato T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. (0815-9319 (Print)).
4 Njie B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. Hepatology 2015; 61:191–199.
5 Lee YT, Geer DA. Primary liver cancer: pattern of metastasis. (0022-4790 (Print)).
6 Jiang XB, Ke C, Zhang GH, Zhang XH, Sai K, Chen ZP, Mou YG. Brain metastases from hepatocellular carcinoma: clinical features and prognostic factors. (1471-2407 (Electronic)).
7 Shimada K, Sakamoto Y, Eskai M, Kosuge T, Morimine C, Ikeda M, et al. Analysis of prognostic factors affecting survival after initial recurrence and treatment efficacy for recurrence in patients undergoing potentially curative hepatectomy for hepatocellular carcinoma. (1088-9265 (Print)).
8 Hong SS, Kim TK, Sung KB, Kim PN, Ha HK, Kim AJ, Lee MG. Extrapleural spread of hepatocellular carcinoma: a pictorial review. (0938-7994 (Print)).
9 Cai M, Shen-Tu Y. [Clinical diagnosis and therapy strategies of lung metastasis]. (1999-6187 (Electronic)).
10 Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, et al. Pre-metastatic niches: organ-specific homes for metastases. (1474-1768 (Electronic)).
11 Altorki NK, Markowitz GJ, Gao D, Port JL, Saxena A, Stiles B, et al. The lung microenvironment: an important regulator of tumour growth and metastasis. Nat Rev Cancer 2010; 19:9–31.
12 Takahashi Y, Ikeda N, Nakajima J, Sawabata N, Chida M, Horio H, et al. Prognostic analysis of surgical resection for pulmonary metastasis from hepatocellular carcinoma. (1432-2323 (Electronic)).
13 Prud’homme C, Deschamps F, Moulin B, Hakime A, Al-Ahmar M, Moalla S, et al. Image-guided lung metastasis ablation: a literature review. (1464-5157 (Electronic)).
14 Lo SS, Loblaw A, Chang EL, Mayr NA, Teh BS, Huang Z, et al. Emerging applications of stereotactic body radiotherapy. (1744-8301 (Electronic)).
15 Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. (1527-7755 (Electronic)).
16 Qin S, Cheng Y, Liang J, Shen L, Bai Y, Li J, et al. Efficacy and safety of the FOLFOX4 regimen versus doxorubicin in Chinese patients with advanced hepatocellular carcinoma: a subgroup analysis of the EACH study. (1549-490X (Electronic)).
17 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. (1533-4406 (Electronic)).
18 Sun J, Shi J, Huang B, Cheng F, Guo W, Lau WY, Cheng S. The degree of hepatic arterial blood supply of portal vein tumor thrombus in patients with hepatocellular carcinoma and its impact on overall survival after transarterial chemoembolization. (1949-2553 (Electronic)).
19 Zhang X, Wu B, Guo Z, Gao Y, Xi W, Yu H, et al. Determination of portal vein tumor thrombus blood supply using in vivo cellular magnetic resonance imaging in a rabbit model. (1179-1322 (Print)).
20 Ando E, Tanaka M, Yamashita F, Kuromatu R, Yutani S, Fukumori K, et al. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. (0008-543X (Print)).
21 Song DS, Bae SH, Song MJ, Lee SW, Kim HY, Lee YJ, et al. Hepatic arterial infusion chemotherapy in hepatocellular carcinoma with portal vein tumor thrombosis. (2219-2840 (Electronic)).
22 Zhu LZ, Xu S, Qian HL. Transarterial embolization and low-dose continuous hepatic arterial infusion chemotherapy with oxalipatin and raltitrexed for hepatocellular carcinoma with major portal vein tumor thrombus. World J Gastroenterol 2018; 24:2501–2507.
23 Xie YA-O, Xiang Y, Sheng JA-OX, Zhang D, Yao X, Yang YA-O, Zhang XA-O. Immunotherapy for hepatocellular carcinoma: current advances and future expectations. (2314-7156 (Electronic)).
24 Zavala VA, Kalergis AM. New clinical advances in immunotherapy for the treatment of solid tumours. Immunology 2015; 145:182–201.
25 Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. (1527-7755 (Electronic)).
26 Borghaei HA-O, Gettinger SA-O, Vokes EA-O, Chow LA-OX, Burgio MA, de Castro Carpeno JA-O, et al. Five-year outcomes from the randomized, phase III trials CheckMate 017 and 057: nivolumab versus docetaxel in previously treated non-small-cell lung cancer. (1527-7755 (Electronic)).
27 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. (1533-4406 (Electronic)).
28 Galle PR, Finn RS, Qin S, Ikeda M, Zhu AX, Kim TY, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. (1474-5488 (Electronic)).