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**

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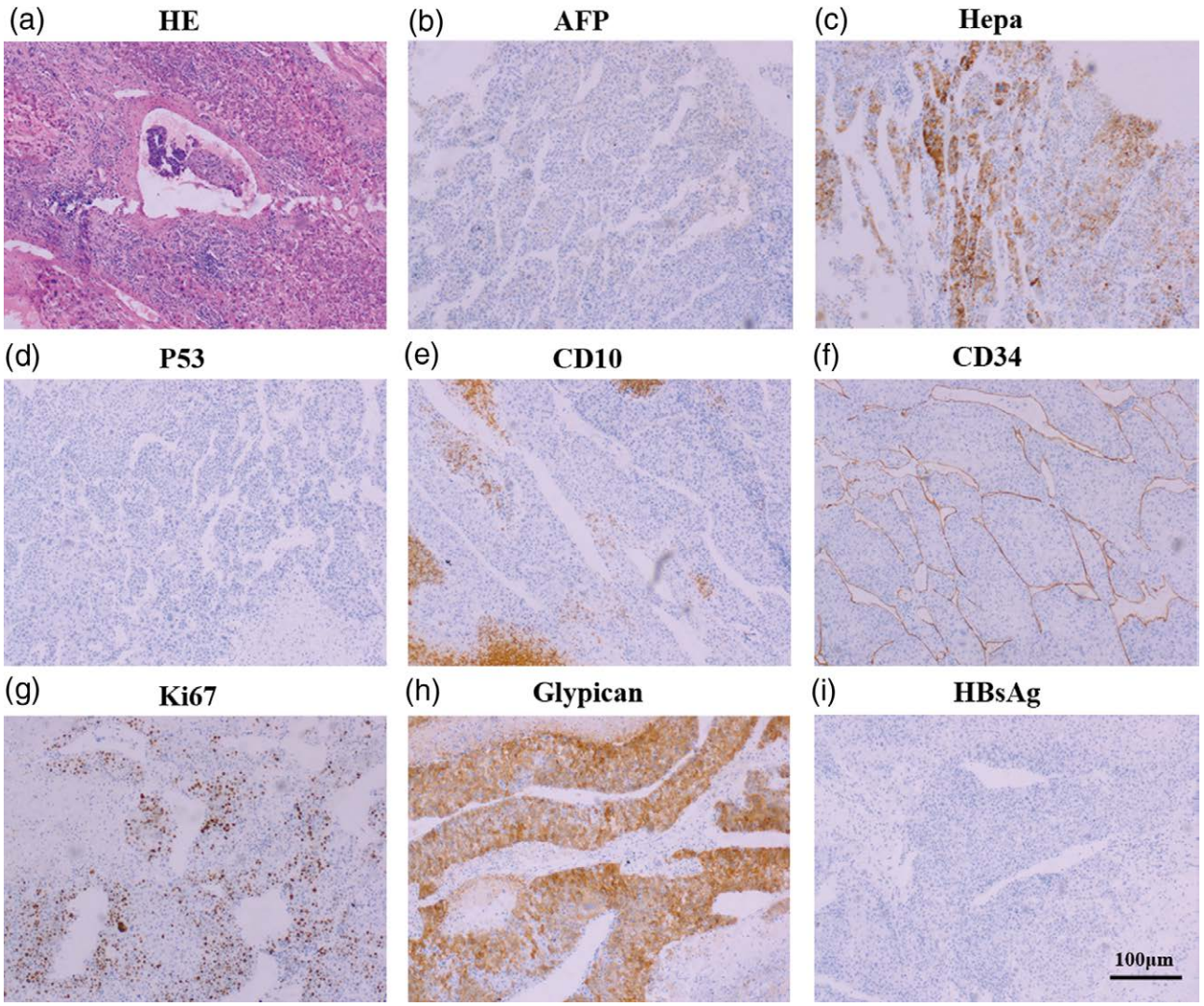
Background

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 5-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 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, 77180.4 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) IIIa, Barcelona Clinic Liver Cancer (BCLC) C]. The clinical

Fig. 1

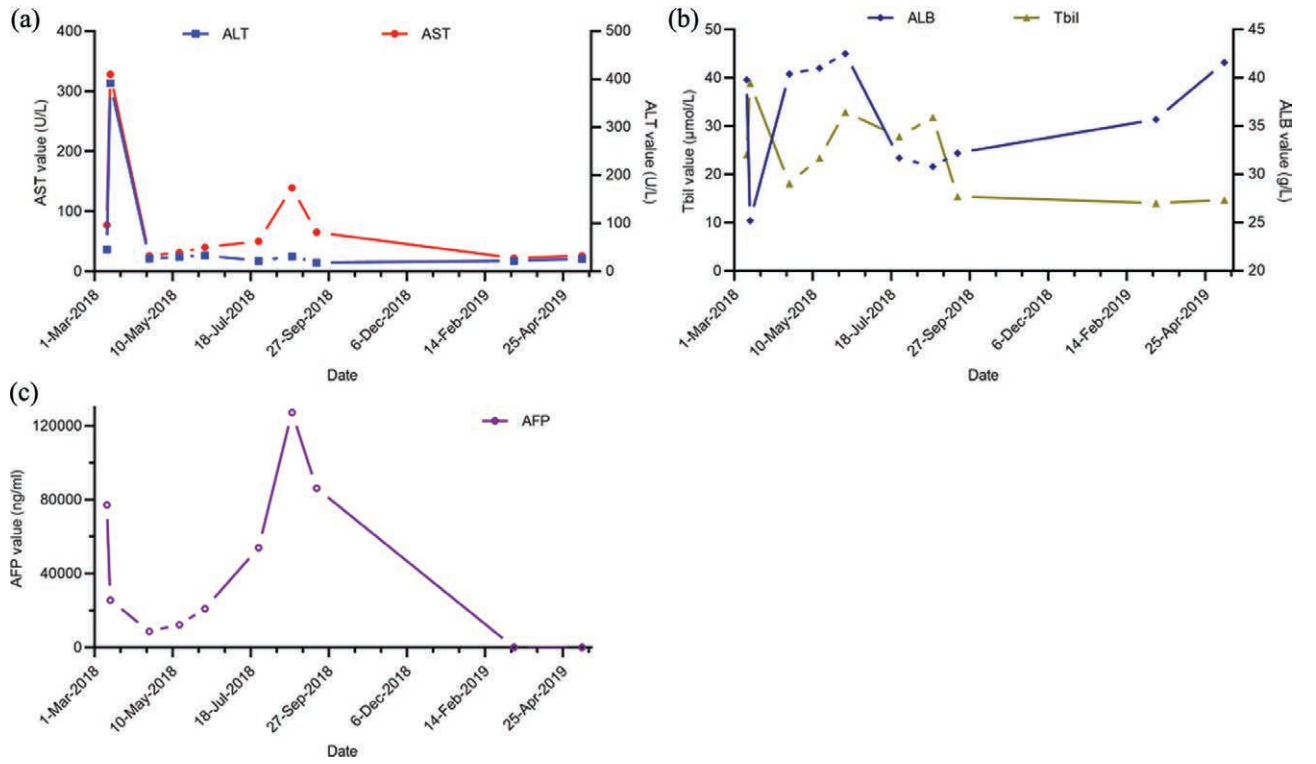


The changes in various indicators with the courses of treatment.

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. 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

Fig. 2



Ultrasound imaging of the portal vein. (a) Preoperative portal vein ultrasound: there was a slightly strong echo mass in the main portal vein, about 13 × 34 mm in size. The right branch was full of blood flow signals, while the left branch was unclear. (b) One month after the operation, portal vein ultrasound showed that the main portal vein carcinoma thrombus was formed and the right portal vein was full of blood signals. (c) Two months after the operation, the portal vein trunk and right branch were filled with blood flow, and no obvious lesion was seen. (d) At 45 months after surgery, the portal vein blood flow is smooth and the blood flow rate is normal.

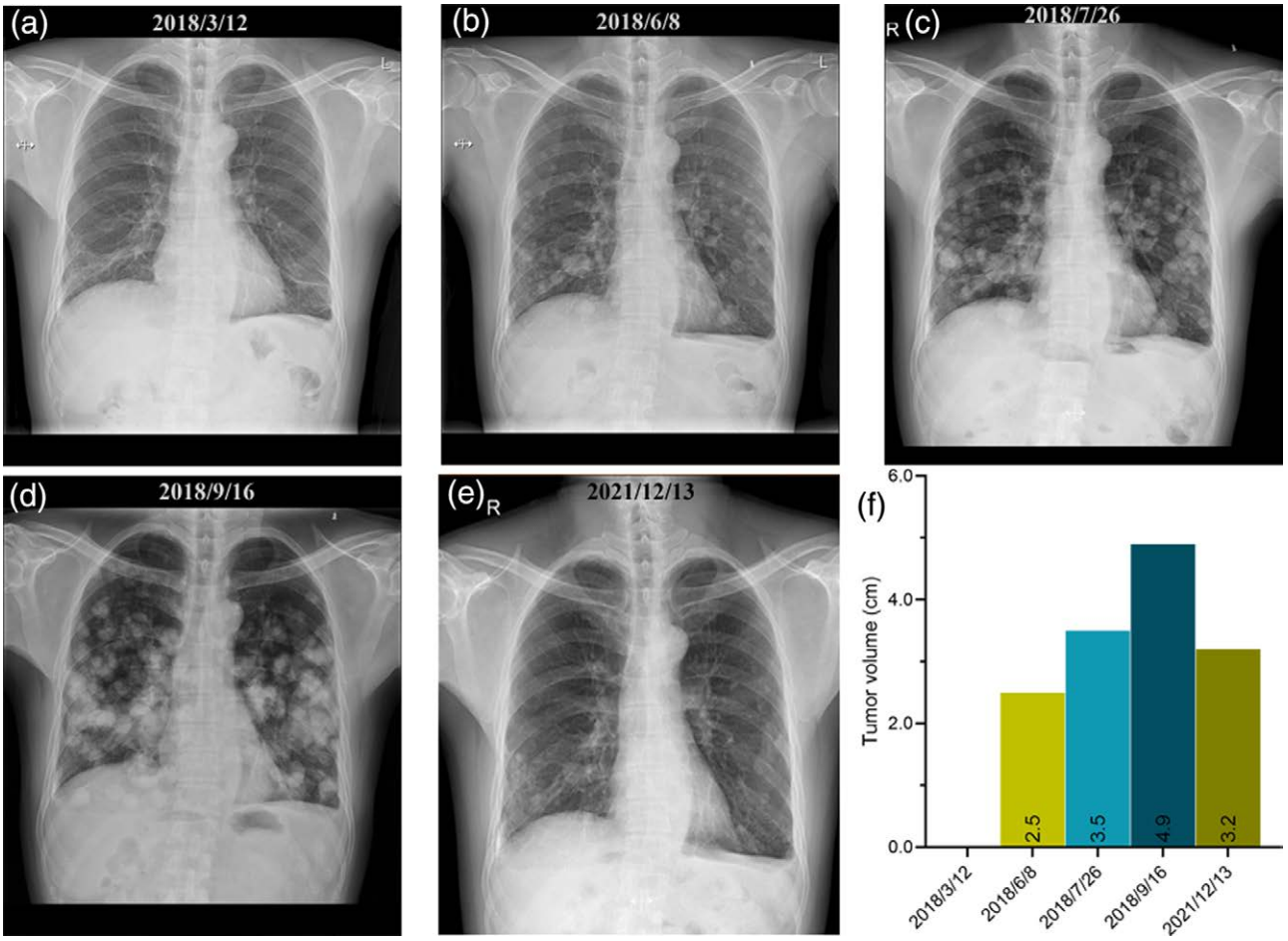
later meanwhile cough symptoms continue to worsen. We changed the protocol again to percutaneous hepatic arteriography and bronchial artery perfusion chemotherapy combined with lobaplatin, epirubicine (EPI), fluorouracil (5-FU) and arsenic trioxide (As_2O_3), yet the AFP level remained 85100.6 ng/ml (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

Fig. 3

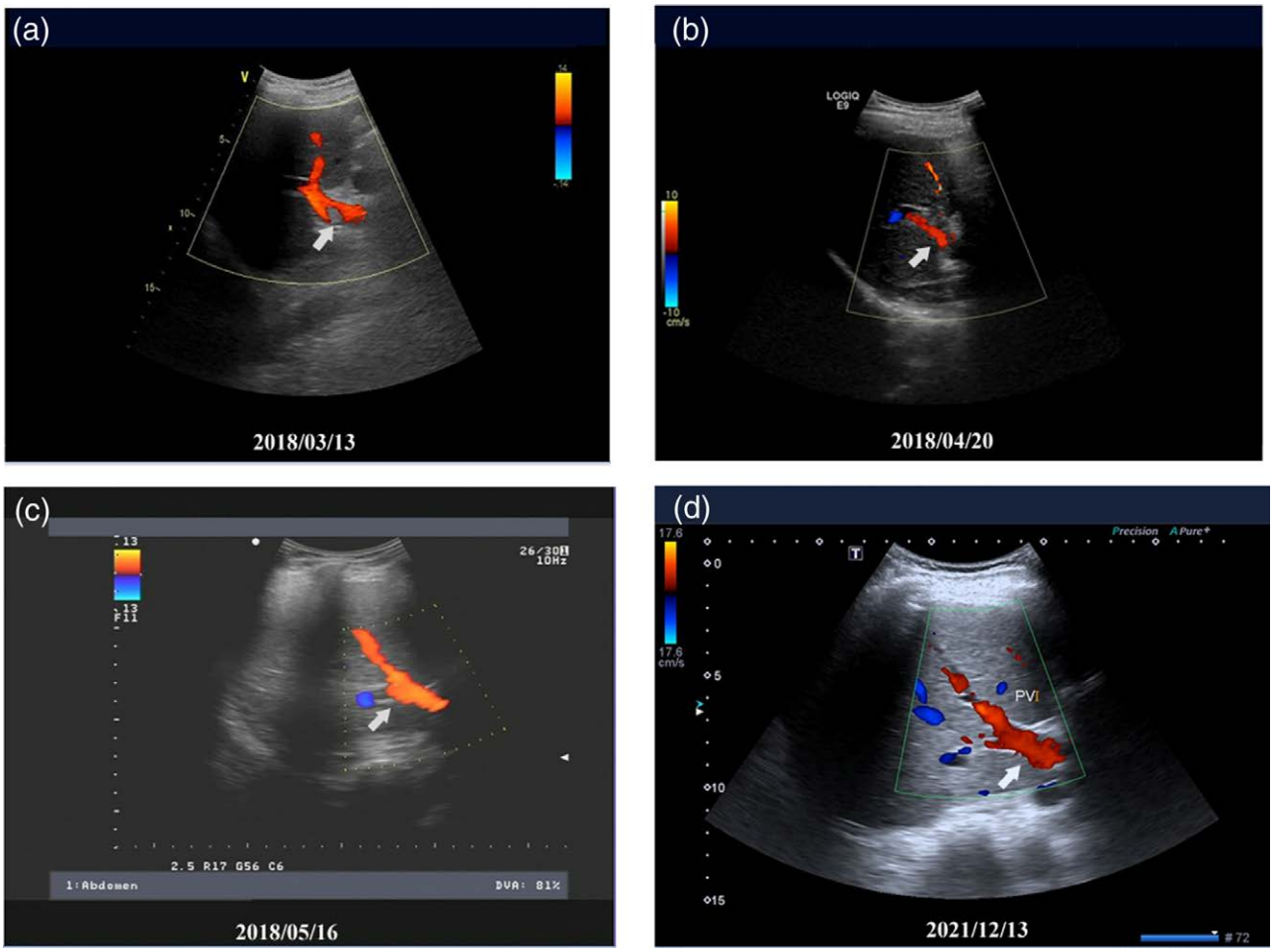


Tumor histopathology. (a) Postoperative pathology: poorly differentiated hepatocellular carcinoma, accompanied by haemorrhage and necrosis, with tumor thrombus visible in the vessels, involving less than 5 vessels. (b) Alpha-fetoprotein expression was positive. (c) Hepatocyte was positive, indicating the origin of hepatocytes. (d) P53 expression was positive and proliferation ability was high. (e) CD10 expression was negative. (f) CD34 expression was positive in sinusoidal endothelium suggesting hepatocellular carcinoma. (g) Ki-67 expression was 50%, indicating active tumor proliferation. (h) Phospholipamide glycol proteoglycan 3 was positive, increasing evidence of hepatocellular carcinoma. (i) Hepatitis B surface antigen was negative, indicating no current infection of hepatitis B.

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

Fig. 4



Changes in chest CT and maximum tumor volume in patients. (a) One month after surgery, there were multiple nodules in both lungs, and the larger ones were located under the pleura of the dorsal segment of the right lower lung, about 2.7 × 2.3 × 1.8 cm. (b) One year after the operation, the lesions increased and enlarged, and the larger ones were located under the pleura of the dorsal segment of the right lower lung, about 3.7 × 3.1 × 3.2 cm. (c) At 19 months after surgery, the lesions of both lung nodules were similar to those before, and the larger ones were about 3.7 × 3.1 × 3.2 cm. (d) At 32 months after surgery, the lesions of multiple metastases in both lungs were reduced compared with before, and the larger ones were about 3.5 × 2.1 × 3.2 cm. (e) At 45 months after surgery, there were multiple metastases in both lungs, some lesions were slightly reduced compared with the previous ones, and the larger ones were located under the pleura of the posterior basal segment of the lower lobe of the right lung, about 2.8 × 1.3 × 1.7 cm.

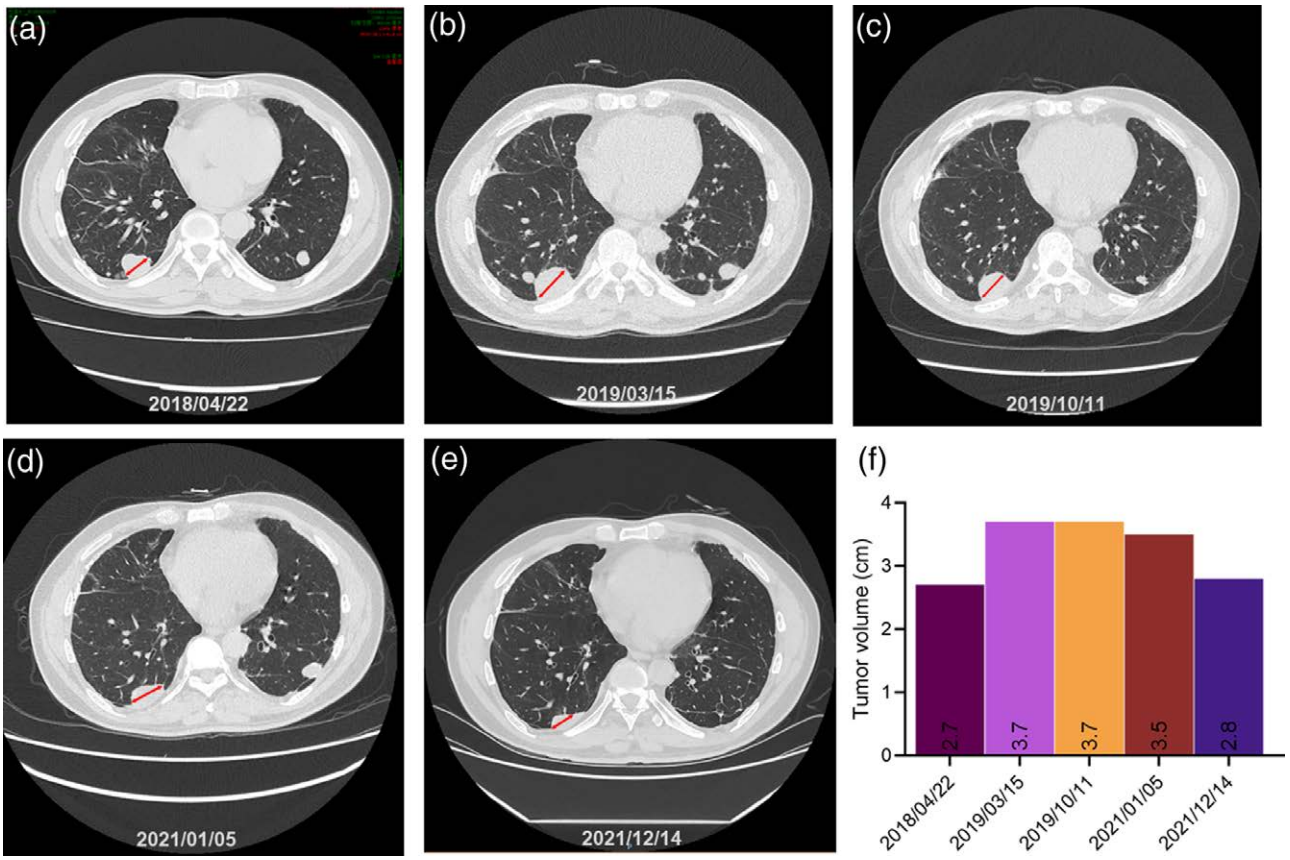
therapy, the chest x-ray shows a keep growing in double lung metastases from 3 months postoperatively to 16 months (Fig. 5) and pulmonary symptoms worsen. The patient who attempted immunotherapy after the launch of immunodrugs experienced a significant reduction in bilateral pulmonary nodules by December 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

Table 1 Therapeutic process

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	Percutaneous hepatic arteriography and bronchial artery perfusion chemotherapy	Lobaplatin 30 mg +EPI 20 mg +5-FU 1g +As_2O_3 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.

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. 4e, 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

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.

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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.

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