Complete cure of a patient with HBV-associated hepatocellular carcinoma with lung metastasis using interferon and survival up to 108 months: A case report and literature review

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Abstract. Hepatocellular carcinoma (HCC) has a poor prognosis due to its asymptomatic onset and susceptibility to metastasis. The survival of patients with advanced HCC is 6-12 months. As a first-line medicine for the control of hepatitis B virus, interferon (IFN) is also capable of inhibiting tumor growth and modulating immunity. However, treatment of HCC with lung metastasis using IFN has been rarely reported. The present study reports the case of one patient with HCC having lung metastasis who underwent a one-time treatment with transcatheter arterial chemoembolization (TACE) and was subsequently completely cured by single peginterferon α 2a (PEG-IFNα2a); and has survived up to 108 months. A 53-year-old male patient diagnosed with HBV-related HCC with lung metastasis underwent TACE using floxuridine (FUDR) 500 mg, cisdiamine dichloroplatinum (CDDP) 20 mg, mitomycin 10 mg, and ultrafluid lipiodol 10 ml, together with local thoracic aorta chemotherapy using FUDR 250 mg and CDDP 20 mg. His metastatic lung cancer aggravated. However, after 9 months of treatment with subcutaneous injections of PEG-IFNα 2a once per week, the metastatic lung foci gradually shrunk until disappearance and the HCC lesion stabilized without progression. According to the World Health Organization criteria for the efficacy of solid tumors, this was a case of complete response. Upon follow-up up to 108 months his metastatic lung cancer had disappeared and HCC did not recur. Therefore, IFN intervention may be an appropriate novel adjuvant therapy for patients with HCC with lung metastasis and requires further attention and study.

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Introduction

Hepatocellular carcinoma (HCC) is the second cause of male cancer-related mortality worldwide. In 2012, 782,500 new patients with HCC and 745,500 cases of death due to HCC were reported, of which 50% were reported in China (1). HCC with extrahepatic metastasis seriously impacts survival, and metastatic lung cancer is the most common extrahepatic metastasis, comprising around 53.8% of all extrahepatic metastasis (2).

No effective therapy is currently available for lung metastatic HCC. According to reports, pneumonectomy is the most effective therapeutic modality. However, prior studies revealed that only 2.6% of patients with HCC with lung metastasis met the operative indication, and surgery benefited only those who had less than four lung metastatic foci with diameters less than 3 cm (3). In China, HCC is mostly secondary to hepatitis B virus-related liver cirrhosis, with multiple lung metastatic foci and poor clinical operability (4). Chemotherapy exhibits certain efficacy for lung metastatic HCC. However, the majority of chemotherapy drugs metabolize in the liver. Hepatotoxicity and bone marrow suppression are the major limitations of chemotherapy. Besides, a universally recognized chemotherapy regimen is still lacking. Molecular targeted therapy of sorafenib is effective for advanced HCC; however, HCC with lung metastasis responds to it poorly (5). Researchers have also explored other therapeutic modalities, such as local radiotherapy, radiofrequency ablation, and so on, but no assertive efficacy has been achieved. Overall, no standardized and effective therapeutic strategy exists for lung metastatic HCC till date.

A recent investigation indicated that interferon (IFN) prolonged survival in patients with HCC who underwent radical resection, and the combination of IFN with cytokine-induced killer adoptive cellular therapy prevented recurrence (6). Complete cure of lung metastatic HCC using single IFN has not been reported till date.

The present study reported one case of HCC with multiple lung metastatic lesions. After one time of transcatheter arterial chemoembolization (TACE) and local chemotherapy via

thoracic aorta, lung metastatic foci evidently increased. Despite that, 4 months of continuous treatment with peginterferon α 2a (PEG-IFN α 2a) led to a gradual reduction in alpha-fetoprotein (AFP) from >1,000 ng/ml to normal prior to treatment and resulted in the gradual disappearance of metastatic lung cancer and stability of HCC lesions without recurrence. Till the date of writing this report, the patient lived a high-quality life for 108 months, reaching a clinical cure according to the World Health Organization (WHO) prognostic criteria.

Case report

A 53-year-old male patient, living in Tianjing, China, had a medical history of diabetes, hepatitis B e antigen-negative chronic hepatitis B, and a family history of hepatitis B and liver cancer (with the death of his mother and one brother from HBV-related HCC), and without a history of blood transfusion. In 2007, the patient started lamivudine, 100 mg qd, for controlling HBV with HBV DNA $5.3x10^6$ cs/ml and alanine aminotransferase 102 U/l. In April 2008, radioimmunoassay estimated a concentration of >1,000 ng/ml of AFP in the patient. Moreover, color ultrasonography revealed a hypoechoic solid mass of size 4.0x4.0 cm^2 in the right anterior lobe of the liver with uneven density and irregular edge, which was considered as HCC. It also showed enlargement of the caudate lobe of the liver, widening of the hepatic fissure, and widening of the portal vein with a diameter of 1.1 cm, in addition to splenomegaly, which was considered as liver cirrhosis. Furthermore, enhanced computed tomography (CT) of the upper abdomen revealed a soft tissue mass with a diameter of 2.26x4.16 cm^2 in the right anterior lobe of the liver, presenting a low-density soft tissue in the plain scanning, mild enhancement of the density in the arterial phase, and yet nonhomogeneous enhancement of the density in the portal phase, along with an evident reduction in the mass density in the equilibrium phase, which was considered as HCC (Fig. 1A). Moreover, chest CT exhibited multiple small nodules in the right inferior lobe of the lung, with a maximum diameter of 0.5 cm, which were considered as metastatic cancer (Fig. 1B). Also, in April 2008, the digital subtraction angiography displayed enlarged and tortuous anterior and posterior branches of the right hepatic artery and the image of a tumor with a diameter 4.1x4.0 cm^2 in the right anterior lobe of the liver in the parenchymal phase, along with five small nodules of <0.5 cm in the right inferior lobe of the lung. In summary, the ultrasound displayed an intrahepatic nodule more than 2 cm in size. The typical dynamic change in the nodule was detected using a dynamic imaging method, presenting vessel density enhancement of the hepatic mass in the arterial phase and rapid elution in the delayed phase under enhanced CT. The AFP level was measured to be >200 ng/ml. According to the 'Clinical Guidelines for Hepatocellular Carcinoma' issued in the year 2005 by the American Association for the Study of Liver Diseases (AASLD), HCC was the definitive diagnosis without the need of biopsy. Gastroscopy indicated mild esophageal varices. Therefore, the preliminary diagnosis was primary HCC, metastatic lung cancer, compensated HBV-related cirrhosis, and chronic hepatitis B. On the request of the patient and his kin as well as signed informed consent, TACE (Fig. 1C) was performed. Specifically, floxuridine (FUDR) 500 mg and cisdiamine dichloroplatinum (CDDP) 20 mg were infused through the proper hepatic artery for chemotherapy, and superselective embolization of the right hepatic artery was conducted using 10 mg mitomycin plus 10 ml of ultrafluid lipiodol. Moreover, 250 mg FUDR and 20 mg CDDP were infused through the bronchial artery of the thoracic aorta at the bifurcation of trachea level for chemotherapy of lung metastatic foci. The patient had HCC with metastatic lung cancer, in phase IV of the TNM staging, at initial presentation. According to the WHO criteria for solid tumor response, TACE for local chemoembolization is a partial remission strategy for treating HCC with lung metastatic foci and the patient survival is expected to be less than 6 months.

In June 2008, following 2 months of TACE, a review check of the patient showed white blood count of $3.00x10^9$/l, platelet count of $71x10^9$/l, and AFP of >400 ng/ml. Also, enhanced CT scanning of the upper abdomen revealed post-TACE change of the soft tissue mass in the right anterior lobe of the liver, good lipiodol sedimentation, and relative stability of the HCC lesion. Chest CT scanning displayed multiple diffuse nodules in the bilateral lung, with the increased number and enlarged volume. Hence, metastatic cancer was considered progressive. The patient refused to take targeted therapy of sorafenib. In systemic consideration of compensated cirrhosis, Child-Pugh A grade, and normal blood routine, in addition to mild esophageal varices by gastroscopy, PEG-IFNα 2a (180 μg qw) was elicited under the informed consent of the patient and his kin. During treatment, regular monitoring of the patient was done, including blood routine, AFP, liver function, and IFN-associated adverse effects, in addition to liver- and lung-imaging changes. The AFP levels gradually reduced with IFN use. In August 2008, 2 months after the IFN intervention, the AFP level was >400 ng/ml, which decreased to 5.8 ng/ml after 4 months, in October 2008. Since then, the AFP level of the patient stayed within the normal range. The patient once had transient leukopenia and neutropenia, but the leukocyte and neutrophil levels resumed to normal in 3 days after temporary subcutaneous administration of the recombinant human granulocyte colony-stimulating factor (rhGCSF) injection, 75 μg per day. IFN was continued, and no other IFN-associated adverse effects were recorded.

In March 2009, 9 months after the IFN intervention, a full hospital review check of the patient showed an AFP of 6.27 ng/ml. An enhanced CT scanning of the upper abdomen revealed the post-TACE change of HCC in the right anterior lobe of the liver. Additionally, chest CT scanning revealed multiple nodules in the bilateral lung, which was considered as metastatic cancer, but with marked improvement than before. Both HCC and metastatic lung cancer met the standard for a complete remission according to the WHO criteria for solid tumor response. In the following 8 years, IFN therapy was continued, and the regular review check displayed stable cancer nodules by enhanced CT scanning of the upper abdomen and chest CT scanning (Fig. 2). In December 2009, HBV mutation was detected in the patient, of which the 204th residue methionine (M) in the YMDD motif of polymerase C was replaced by isoleucine (I), with HBV DNA of $2.7x10^4$ cs/ml. The situation improved after adding adefovir dipivoxil combined with lamivudine to control the

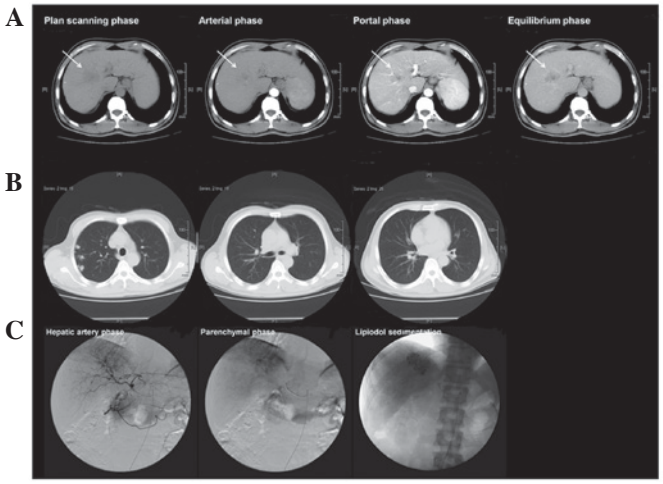

Figure 1. Enhanced CT scanning of the upper abdomen and chest CT scanning prior to treatment and TACE imaging. (A) In April 2008, a soft tissue mass 2.26x4.16 cm^2 in size, with a low density was displayed in the right anterior lobe of the liver. This was observed in the plain scanning, mild enhancement of density in the arterial phase and the nonhomogeneous enhancement of the density in the portal phase, as well as with an evident reduction in the mass density in the equilibrium phase. (B) Chest CT exhibited multiple small nodules in the right inferior lobe of the lung with a maximum diameter of 0.5 cm, which were considered as metastatic cancer. (C) In April 2008, the digital subtraction angiography displayed enlarged and tortuous anterior and posterior branches of the right hepatic artery, and the image of a tumor with 4.1x4.0 cm^2 in size in the right anterior lobe of the liver in the parenchymal phase, along with five small nodules of <0.5 cm in the right inferior lobe of the lung, which was considered as HCC with metastatic lung cancer. Under the request of the patient and his kin TACE was performed. A total of 500 mg FUDR and 20 mg CDDP were infused through the proper hepatic artery for chemotherapy and superselective embolization of the right hepatic artery was conducted using 20 mg mitomycin 20 mg plus 10 ml ultrafluid lipiodol. In addition, 250 mg FUDR and 20 mg CDDP were infused through the bronchial artery of the thoracic aorta at the bifurcation of trachea level for chemotherapy of lung metastatic foci. After TACE, good lipiodol sedimentation was observed in the lesion in the right anterior lobe of the liver. CT, computed tomography; TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma; FUDR, floxuridine; CDDP, cisdiamine dichloroplatinum.

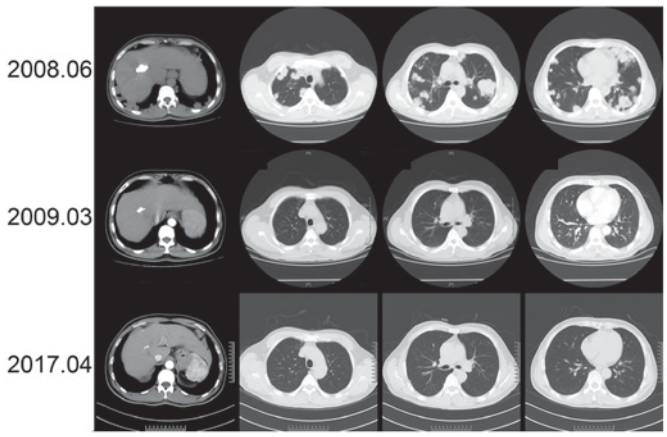

Figure 2. Change in lesions in the liver and lung after TACE treatment. Following TACE treatment, a review check with enhanced CT scanning of the upper abdomen revealed lipiodol sedimentation in the primary cancer nodule, which decreased each year and stable nodules without progression, in addition to the negative incidence of the new intrahepatic lesion. In June 2008, 2 months following TACE, a chest CT scanning revealed multiple diffuse and scattered nodules in the bilateral lung, which increased in number and volume compared with those detected in April 2008. Metastatic lung cancer was considered progressive and interferon intervention was elicited. In March 2009, 11 months after TACE and 9 months after interferon therapy, a chest CT displayed multiple nodules in the bilateral lung with a decrease in number and evident reduction in volume. Metastatic lung cancer was considered a retraction. A later review check with a CT still exhibited micronodules in the bilateral lung, in a stable state without recurrence. TACE, transcatheter arterial chemoembolization; CT, computed tomography.

virus. In February 2014, the patient terminated antiviral drugs on his own accord. After 2 months, on April 23, 2014, the review check showed HBV DNA of 9.65x10^8 cs/ml, and the YMDD motif of the polymerase C was resumed to wild type. Antiviral therapy with entecavir was given till date, and HBV DNA was detected to be negative (Fig. 3). Also, the AFP levels were monitored to be normal. No other HCC-related therapy was enforced ever since (Fig. 4). In April 2017, the review check showed AFP of 1.32 ng/ml, hepatitis B surface antigen (HBsAg) of 45.43 IU/ml, and negative HBV DNA. An enhanced CT scanning of the upper abdomen displayed a stable HCC nodule, and the chest CT revealed micronodules in the bilateral lung. According to the WHO criteria for solid tumor response, the patient reached a complete remission and survival of up to 9 years, with a good quality of life (QOL) reflected by the Karnofsky Performance Scale score of 100, performance status grade 0, and QOL score of 60. Currently, the patient sticks to the average follow-up, once every 3-4 months, and his general condition, cancer status, and potential adverse effects are being monitored (Tables I and II). Continuous attention is being paid to the disease status of the patient.

Discussion

HCC metastasis and recurrence severely impact patient survival and QOL. However, no standardized effective therapy strategy is available for lung metastatic HCC till date. Personalized therapy deserves further exploration. Radical surgery is recognized as the cure, but the number of patients who met the operative indication is limited. Systemic chemotherapy is also one of the common therapy strategies, but it is not extensively appreciated because it deteriorates cancer recurrence and showed no effect on survival improvement in postoperative patients with HCC and cirrhosis (7). Molecular targeted therapy of sorafenib is effective for advanced HCC; however, HCC with lung metastasis responds to it poorly (5). Additionally, the existence of multidrug resistance gene leads to poor chemotherapeutic efficacy and accelerated adverse effects, imposing risks on patient's safety.

In previous studies, the prognosis of HCC with lung metastasis was poor, but administering IFN was beneficial (Table III) (8-15). A recent report documented a successful cure of lung metastatic HCC by chemotherapy, in which Japanese researchers applied S-1 (the oral fluoropyrimidine), a complex of tegafur, gimeracil, and oteracil potassium, combined with IFNα to treat 11 patients who lived for more than 1 year. One of them lived for more than 5 years with the disappearance of multiple metastatic lesions (16). From the overall perspective, no standardized effective strategy still exists for systemic chemotherapy, and adequate evidence-based analysis is lacking. The patient in the present case study lived up to 108 months without cancer, taking no

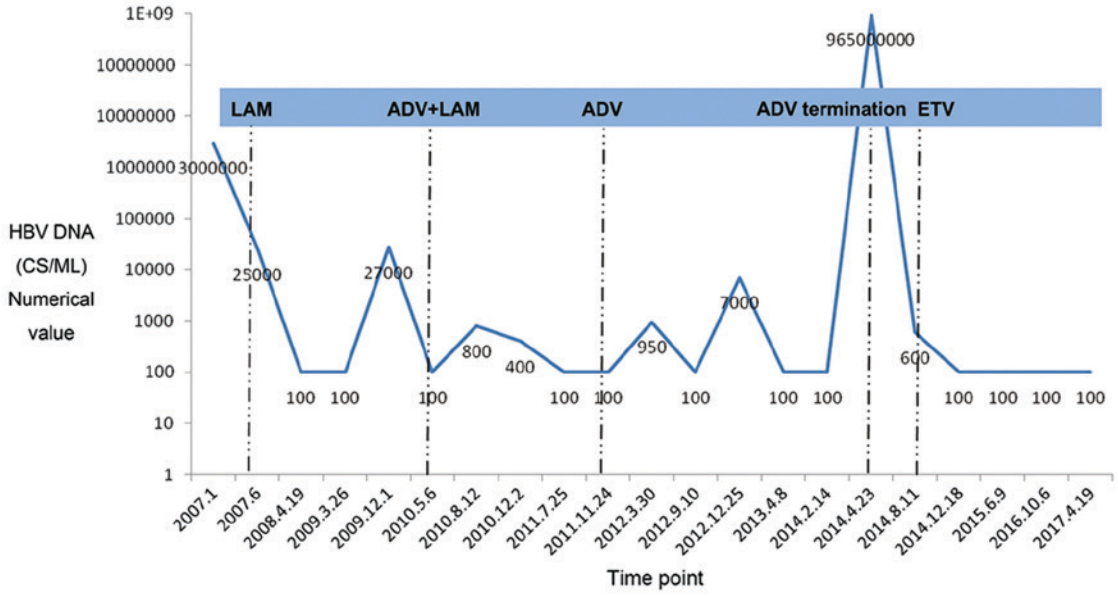

Figure 3. Antiviral drug (nucleoside/nucleotide analogues) intervention and change in HBV DNA levels. ADV, Adefovir dipivoxil; ETV, entecavir; LAM, lamivudine; HBV, Hepatitis B virus; CS/ML, copies/ml.

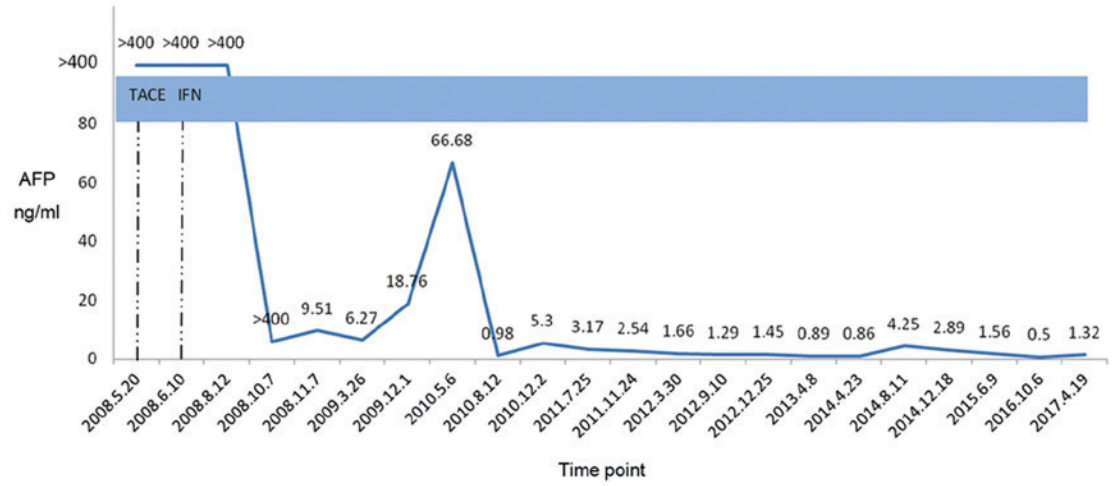

Figure 4. HCC therapy process and changes in AFP levels. HCC, hepatocellular carcinoma; AFP, α-fetoprotein; IFN, interferon; TACE, transcatheter arterial chemoembolization.

subsequent chemotherapy after TACE, except IFN. This was not reported before and deserved further exploration.

IFN is a multifunctional cytokine with antiviral and antitumor activities, which is probably more beneficial for HBV-related patients with HCC. After surgical resection of HCC, IFN is the most effective adjuvant therapeutic modality for survival improvement compared with other common adjuvant therapeutic strategies for HCC (6). A variety of meta-analyses indicated that IFN improved the nonrecurrence survival and overall survival following surgical resection of virus-related HCC (17-19). Moreover, IFN intervention remarkably attenuated mortality and recurrence in HBV-related patients with HCC having a therapeutic history of TACE (20). In the patient in the present case study, TACE was used comprising CDDP and FUDR for HCC, and CDDP/FUDR achieved a good tumor response (21). Because of the local and one-time therapy using CDDP/FUDR, IFN intervention was speculated to be the key to the successful cure of patients based on several potential reasons as follows.

First, IFN imparts direct and indirect antitumor effects. From one aspect, IFN acts directly on tumor cells, inhibiting cell proliferation and promoting apoptosis possibly via the mechanisms as follows: i) it is mainly involved in biological behaviors, such as proliferation, differentiation, and apoptosis, via a Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway (22); ii) it promotes apoptosis of the HCC cells via transactivation of P38/mitogen-activated protein kinase pathway (23); iii) it activates p63 in the S/G2/M phases of the cell cycle and causes cells to remain quiescent in phase G1, thus inducing apoptosis of the HCC cells (24) and iv) it induces autophagy via JAK/STAT and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathways and is crucial in the inhibition of cell proliferation (25). From another aspect, IFN

Table I. Monitoring of interferon therapy-related adverse effects during treatment.

Follow up date (month/year)	WBC (3.5-9.5)x10^9/l	PLT (100-300)x10^9/l	IRT	Ca (2.03-2.54) mmol/l	P (0.90-1.34) mmol/l	TSH (0.27-4.2) mIU/l	CD4 (32.8-52.8)%	CD8 (19.7-38.9)%	Gastroscopy
04/2008	3.3	67	All negative	-	-	-	-	-	EV, Li, F1, RC(-)
06/2008	3	71	-	-	-	-	42.8	41.1	-
04/2009	3.01	83	All negative	2.39	0.66	-	28.7	25.4	-
05/2010	3.81	93	-	-	-	-	36.3	31.3	-
12/2010	3.57	86	-	-	-	-	-	-	EV, Lmi, F2, RC(-)
07/2011	4.13	107	-	-	-	-	28.4	29.1	-
03/2012	3.71	140	-	-	-	-	-	-	-
12/2012	4.96	112	-	-	-	-	-	-	EV, Lmi, F2, RC(-)
04/2013	5.25	119	All negative	2.22	0.6	-	35.1	33.1	-
08/2014	4.77	104	-	2.19	1.03	0.21	-	-	-
12/2014	3.87	101	-	2.08	0.64	-	-	-	Esophagitis, superficial gastrotis
06/2015	4.06	88	All negative	2.08	0.81	-	-	-	-
10/2016	3.54	97	All negative	-	-	0.75	-	-	-
04/2017	3.63	89	All negative	2.19	0.76	-	-	-	-

WBC, white blood cells; PLT, platelets; IRT, immunologic-related test; Ca, serum calcium; P, serum phosphorus; TSH, thyroid-stimulating hormone; CD, cluster of differentiation; EV, esophageal varices; IRT included antinuclear antibody, anti-mitochondrial antibody, anti-mitochondrial antibody M2 subtype, SP100 antibody, anti-glucoprotein 210 antibody, anti-SSA antibody, anti-SSB antibody, anti-dsDNA antibody, anti-smooth muscle actin antibody, anti-liver kindey microsome antibody, anti-soluble liver antigen antibody, anti-Sm antibody, IgE, IgG, IgA and IgM.

Table II. Clinical follow-up records of potential adverse effects during IFN therapy.

	IFN-associated adverse effects	Follow-up and management
Influenza-like symptoms	Fever (T>37.3˚C)	Transient, disappeared after 1 week
	Headache	Transient, disappeared after 1 week
	Muscle and joint sore	Transient, disappeared after 1 week
	Whole-body discomfort	Transient, disappeared after 1 week
Gastrointestinal reactions	Nausea, vomiting, inappetence	No occurrence
Changes in the skin and hair	Hair loss	Evident in the first year and stable in the following years
	Whole-body itching, rash	No occurrence
Symptoms of bone marrow suppression	Leucopenia	Transient, no interference with use after symptomatic management
	Thrombocytopenia	Transient, no interference with use after symptomatic management
Symptoms of the nervous system	Fatigue, insomnia, indifference, lack of initiative, depressed to suicide	No occurrence
Thyroid dysfunction symptoms	Change in T3, T4, and TSH	No occurrence
	Thyroid autoimmune antibody	No occurrence
Autoimmunity diseases	Diabetes	Stable blood glucose level
	Thyroiditis, autoimmune hepatitis, biliary cirrhosis	No occurrence
Ocular abnormalities	Infraorbital hemorrhage	No occurrence
	Retinal hemorrhage	No occurrence
Hearing impairment	Tinnitus, hearing loss	No occurrence
Cardiovascular system	Arrhythmia, pericarditis	No occurrence
Respiratory system	Interstitial pneumonia, pulmonary embolism	No occurrence

IFN, Interferon; TSH, thyroid-stimulating hormone.

exerts an indirect antitumor effect by activating host antitumor immune response via mechanisms as follows: i) it transactivates PI3K/Akt signaling pathway and thus activates natural killer (NK) cells to execute antitumor activity (26); ii) it enhances NK cell-mediated antitumor immunity via activation of host dendritic cells (27); iii) it promotes tumor-specific $CD8^+$ T cells, thus increasing the response of cytotoxic T lymphocytes to enhance antitumor activity (28) and iv) it inhibits proliferation of regulatory T cells (Treg) and attenuates Treg-mediated immune suppression to play an indirect antitumor role (29).

Second, IFN inhibits metastatic lung foci. IFN intervention could not only continuously inhibit HCC growth but also block the proliferation of the metastatic foci in the lung. The epithelium mesenchymal transition (EMT) is closely associated with tumor metastasis, and matrix metallopeptidase 9 (MMP-9)-mediated EMT is essential in the process, while downregulation of MMP-9 can hinder HCC metastasis (30). Macrophage in the lung secretes MMP-9 to promote the proliferation and migration of metastatic lung foci, and IFN intervention decreases MMP-9 levels to control metastatic lung foci (31). IFN also inhibits metastasis and recurrence of HCC via downregulation of VEGF-mediated angiogenesis (32).

Long-term IFN therapy also benefits patients (33). Drug termination in the patient who underwent IFN antitumor therapy elicits upregulation of MMP-9 and macrophages in the lung, explaining the increase in recurrence and lung metastasis after drug termination according to clinical observations (34). Of course, attention should be paid to adverse effects of IFN therapy, for example hematologic disorder and influence on thyroid functions and nervous system. Intolerance to these adverse effects interferes with the extensive and long-term application of IFN in patients with HCC. With an optimistic attitude toward life, the patient in the present study took IFN for a long duration. Close monitoring of the changes in blood routine, blood sugar, thyroid function, and immunity-related tests exhibited negative abnormality. The patient responded and tolerated well to IFN intervention, which was also considered as a critical element for benefits to the patient.

Finally, the antiviral activity of IFN likely benefits patients. The disappearance of HBsAg is the ultimate goal of chronic hepatitis B therapy, which contributes to the control of the incidence rate of HCC. When IFN decreases the HBV DNA levels, it also regulates the immune response leading to limitation of HBsAg, and its combinatory therapy with nucleotide analogues probably imposes a synergistic effect on the maximal reduction in the prevalence rate of HBV-related HCC (35). In the present study, the patient once had the HBsAg level as high as 25,000 IU/ml during the last 8 years or more, which was reduced to 45.43 IU/ml (current) by the combinatory antiviral therapy of IFN with various nucleotide analogues, reflecting good immunological control of HBV infection in the patient system. Although the nucleotide analogue was capable of improving survival in patients with HCC, it could

Table III. Previous reports of cases with interferon treatment for hepatocellular carcinoma with lung metastasis.

Author, ref	Age/sex	History	Location of HCC	Treatment for HCC	Recurrence time	Recurrence site	Treatment for recurrence	Type of interferon	Other therapy	Prognosis
Katsura *et al* (8)	77/male	NA	Left lobe	TACE and left hepatic lobectomy	7 months	Multiple bilateral lungs	S-1	IFN	No	Alive with the disease details were not shown, alive with good condition without recurrence and progression of tumors
Oh *et al* (9)	49/male	CHB, cirrhosis, RFA for a single HCC (4 cm, segment 7)	Intrahepatic recurrence of HCC with extensive lung metastases	HAIC comprising epirubicin and cisplatin, and systemic infusion of 5-FU	13 months	A single small HCC lesion in the left lobe	HAIC, percutaneous intratumoral chemoinjection therapy with 5-FU and IFN-γ	IFN-γ	No	Disease-free intervals for the liver and lung were 41 and 54 months, respectively
Kilickap *et al* 10)	37/male	CHB, HCC	Right lobe, 49x61 mm	Right hepatic lobectomy	1 month	Thoracic 6-8 vertebrae	T6-8 laminectomy,	IFN-α	No	Alive without disease on lamivudine and IFN-α, disease-free for 3 years; followed up about 10 years after diagnosis
					3 years 3 months	The left lower lobe of the lung, 1 cm	Local radiotherapy Resected lung metastasis	IFN-α	Lamuvidine	
					4 years finding but stable, progression on 5 years 6 months	The left kidney, from 13x13 mm increasing to 25 mm	Partial nephrectomy	Pegylated IFN-α	Lamuvidine	
Tanaka *et al* (11)	60/male	Hepatitis C	Segment 3, 44 mm in diameter	Partial hepatectomy	9 months after the surgery	Intra abdominal solitary lymph node metastasis	Removal of the lymph node	NA		Alive with no recurrence 19 months, 30 months after the initial operation
Nakamura *et al* (12)	54/male	PVT and multiple intrahepatic metastases	The bilateral lobes of the liver	Extended left lobectomy, intra-arterial 5-FU infusion chemotherapy, IFN-α to treat the lesions in the residual liver	7 months	Recurrent tumors in the spleen and residual liver	S-1	IFN-α		Alive with no recurrence 32 months after initial hepatic resection
						Recurrent tumors in the lung	S-1, resected	IFN-α		

Table III. Continued.

Author	Age/sex	History	Location of HCC	Treatment for HCC	Recurrence time	Recurrence site	Treatment for recurrence	Type of interferon	Other therapy	Prognosis
Nakamura *et al* (13)	56/male	PVT and multiple intrahepatic metastases	Extended left lobectomy and a partial resection of the liver	Extended left lobectomy and a partial resection of the liver, after two weeks, intra arterial 5-FU infusion, IFN-α	4 months	Hepatic vein tumor thrombus, inferior caval vein	TS-1	IFN-α		NA
					8 months	Mutiplle pulmonary metastases				
Nakamura *et al* (14)	52/male	NA	Right lobe	Right lobectomy	5 months	Multiple recurrences in the live and lung	TAE, UFT and IFN-α	IFN-α and IFN-β	5-FU/ CDDP/ IFN-α, TS-1/ IFN-β	Survived 31 months with no disturbance in quality of life
Kanda *et al* (15)	64/male	HCC with lung metastasis	NA	γ-interfeorn and mitoxantrone	NA	NA	NA	IFN-γ	HCFU 400 mg/ body everyday for 8 months	Still alive

TACE, transcatheter chemoembolization; TAE, transcatheter embolization; RFA, radiofrenquency ablation; HAIC, hepatic arterial infusion chemotherapy; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; PVT, portal vein thrombus; NA, not available; IFN, interferon; 5-FU, 5-fluorouracil; TS-1, Gimeracil and Oteracil Porassium Capsules; UFT, Tegarur-uracil, Ftoyafuy; CDDP, cisdiamine dichloroplatinum.

not treat HCC on its own. Therefore, IFN was believed to be indispensable in fighting against HBV and HCC, which was probably the essential cause leading to the complete clinical cure and high QOL for the patient. Until now, this is the only case reported with a survival of 108 months and with regular follow-up. This patient was followed up regarding disease progression and change.

In summary, this study provided a novel idea for treating patients with HCC having lung metastasis, particularly HBV-related HCC. IFN intervention, as the main adjuvant therapy, resulted in complete disappearance of metastatic lung cancer and led to stable HCC without progression, in addition to a complete clinical cure and long-term survival. Prior to treatment, if HBV whole-genome sequencing from the patient or genetic test of the HCC tissue had been performed, or the immune state of the patient had been uncovered, for example, the measurement of IFN receptors, it would have helped to sort out the beneficial factors of IFN cure of HBV-related HCC. Given IFN exerts anti-HBV and antitumor effects, long-term IFN intervention is a promising strategy as a critical adjuvant therapy for HBV-related HCC with lung metastasis, which is worth studying further. Also, the IFN dose and treatment course requires attention, together with its safety and applicable population.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FW observed the patient's condition, collected clinical data and wrote the manuscript. HML, YL, TH, HL, FL and YG participated in the clinical treatment and follow-up record of the patient over the past 9 years. KJ conducted the TACE treatment and image data follow-up of the patient. FMW decided on the patient diagnosis and treatment as well as the design and revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics committee of Tianjin Third Central Hospital in accordance with the ethical standards mentioned in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from the patient included in the study.

Patient consent for publication

Informed consent was obtained from the patient for the publication of their data and associated images.

Competing interests

The authors declare that they have no competing interests.

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