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Immune Checkpoint Inhibitor as a Therapeutic Choice for Double Cancer: A Case Series

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Abstract. *Background: Hepatocellular carcinoma (HCC) occasionally presents with simultaneous or metachronous primary malignancies of other organs. Despite the limited scope of cytocidal anticancer drugs or molecular targeted agents, immune checkpoint inhibitors (ICIs) can still be used for various malignancies. Here, we present cases of double cancers including HCC treated with ICIs. Case Report: Case 1: A 70-year-old man with lung cancer and 80-mm HCC underwent nivolumab therapy. The sizes of both cancers remained constant for nine months. Case 2: A 58-year-old man with pharyngeal cancer and HCC. Nivolumab was administered, but was withdrawn after one session because of progressive disease. Case 3: A 71-year-old man with a 5 cm HCC invading the inferior vena cava, and early esophageal cancer. HCC showed a significant volume reduction and esophageal cancer demonstrated slight improvement by atezolizumab and bevacizumab therapy. Conclusion: A combination therapy including ICI is a promising treatment option for HCC with concurrent malignancies.*

Immune checkpoint inhibitors (ICIs) have been used to treat various malignancies because they target the immune system, rather than directly affecting cancer cells. Atezolizumab is a programmed cell death ligand (PD-L1) antibody that, along with bevacizumab, was recently approved for hepatocellular carcinoma (HCC) (1). It has also been approved for unresectable non-small cell lung cancer (2), small cell lung cancer (3), and triple-negative breast cancer (4). Nivolumab is a PD-1 antibody that has been approved for melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, gastric cancer, malignant pleural mesothelioma, esophageal cancer, and colorectal cancer (5).

Multiple primary malignancies (MPM) refer to the occurrence of multiple primary cancers derived from different organs (6, 7). Chemotherapy has been used to treat multiple unresectable cancers that developed simultaneously (8). Despite the limited scope of cytocidal anticancer drugs or molecular targeted agents (MTA), ICIs can still be used for various malignancies. Therefore, ICI is a strong first-line drug candidate for unresectable double cancer. Here, we present cases of MPM, consisting of HCC and squamous cell carcinoma (SCC), treated with ICIs.

Case Report

Case 1. A 70-year-old man underwent chemoradiotherapy for SCC of the lung three years ago, and a complete response was achieved. Computed tomography (CT) showed an 8.0 cm tumor in the left lobe of the liver. He was diagnosed with HCC because of findings of homogenous hyperenhancement in the arterial phase and hypoenhancement in the portal phase on contrast-enhanced CT. After two sessions of conventional transarterial chemoembolization (TACE), the HCC underwent necrosis, but its diameter remained constant. Moreover, severe post-embolization syndrome developed after TACE.

Lung cancer recurrence was detected, and nivolumab (240 mg) was administered every three weeks. The sizes of the HCC and lung cancer remained constant for nine months. The

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Key Words: Immune checkpoint inhibitor, multiple primary malignancies, hepatocellular carcinoma, squamous cell carcinoma, nivolumab, atezolizumab.

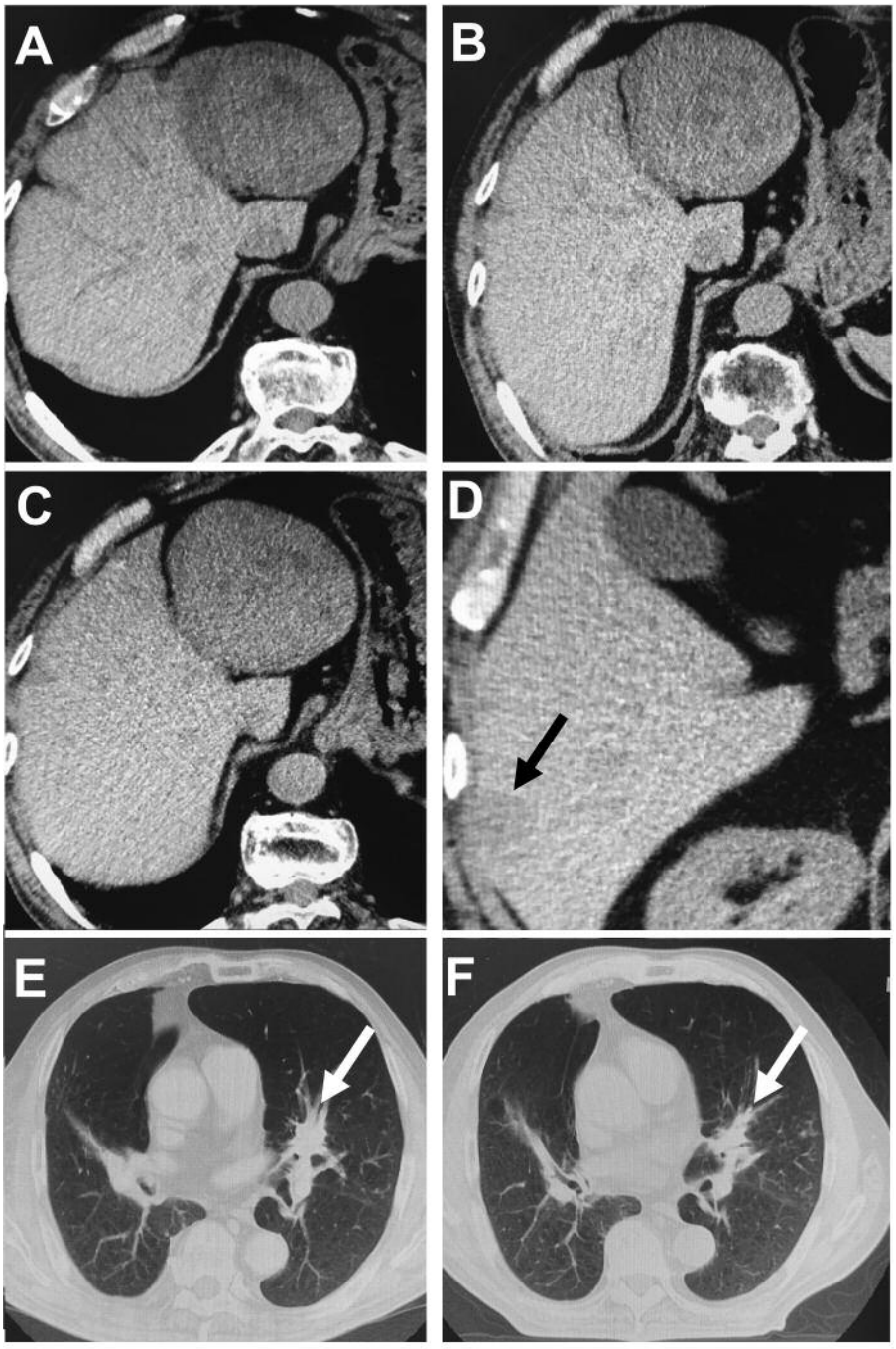

Figure 1. *Case 1. (A) CT showed an 8.0 cm tumor in the left lobe of the liver. (B) The sizes of the HCC remained constant after three months. The main HCC tumor enlarged to 9.0 cm (C), and multiple intrahepatic metastases appeared in the right lobe (arrow) after nine months (D). (E) Lung cancer recurrence was detected at the left pulmonary hilum (arrow). (F) It remained constant after three months (arrow).*

main HCC tumor enlarged to 9.0 cm, and multiple intrahepatic metastases appeared in the right lobe. The lung cancer tumor also enlarged. Furthermore, progressive rectal cancer was detected by colonoscopy following melena (Figure 1).

Case 2. A 58-year-old man underwent chemoradiotherapy for SCC of the oropharynx two and a half years prior. Combination therapy, consisting of cetuximab, cisplatin, and 5-Fluorouracil, resulted in progressive disease.

However, HCV eradication therapy with interferon achieved a sustained viral response. A 3.4 cm-HCC was detected in segment 8, two years ago. After three rounds of conventional TACE, the HCC decreased to 1.4 cm. Stereotactic body radiotherapy (SBRT) was performed six months previously. HCC decreased in size, although the vascularity remained.

Nivolumab (240 mg) was administered but was withdrawn after one session because of progressive disease (Figure 2). Subsequently, the patient underwent paclitaxel therapy. The oropharyngeal cancer partially responded, but the HCC enlarged by 5 cm and infiltrated the anterior branch of the portal vein. SBRT was performed for HCC, but it continued to enlarge. The patient died 15 months after nivolumab therapy.

Case 3. A 71-year-old man with chronic hepatitis B was admitted to our institution for the evaluation of a hepatic tumor. Eleven years ago, a 2.5-cm hepatic tumor, localized in segment 5 was resected. The pathological diagnosis was poorly differentiated HCC. He also underwent a partial pneumonectomy of segments 3, 5, and 9 of the right lung for SCC five years prior. The resected specimen was identified as a SCC with low PD-L1 expression. S-1 was administered for one year postoperatively, and recurrence has not been observed.

Contrast-enhanced ultrasonography, CT, and magnetic resonance imaging revealed a 5-cm tumor in segment 4, invading the inferior vena cava through the right hepatic vein, with hyperenhancement in the arterial phase and hypoenhancement in the portal phase.

Upper esophagogastroduodenoscopy (EGD) revealed a shallow depressed lesion in the upper esophagus. The pathological diagnosis of the biopsy specimen was SCC.

Since HCC was in advanced stage, the patient received combination therapy with atezolizumab and bevacizumab. The contrast-enhanced CT after two months showed a partial response, and the alpha-fetoprotein decreased from 167.0 to 6.4 ng/ml. The des-gamma-carboxy prothrombin also decreased from 108 to 14 mAU/ml. EGD was performed seven months after the initiation of chemotherapy and resulted in slight improvement compared to the baseline findings. The patient has remained healthy nine months after the initiation of chemotherapy (Figure 3) (Table I).

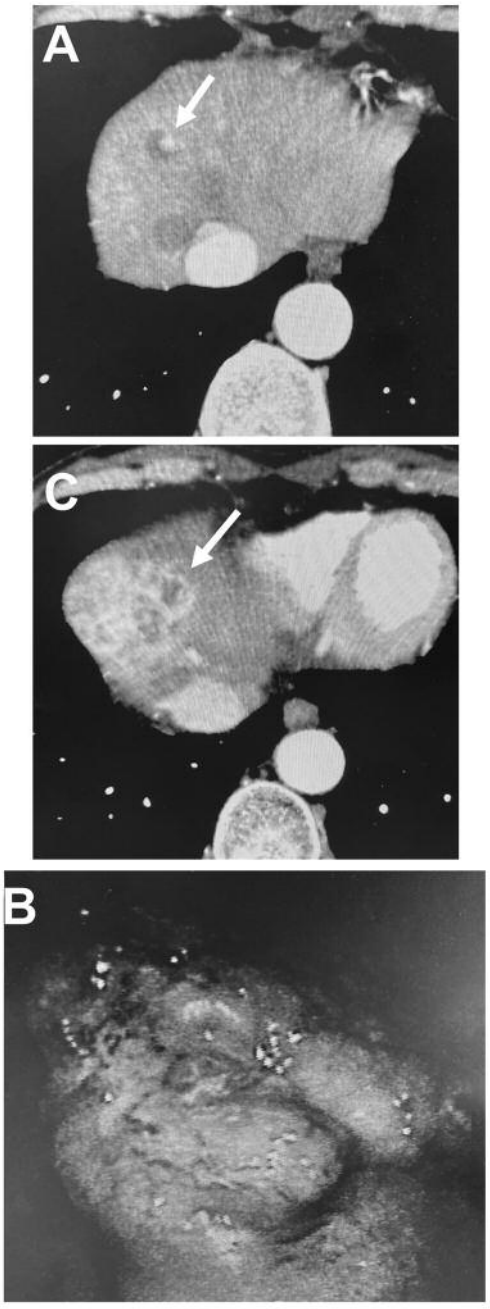

Figure 2. *Case 2. (A) HCC decreased in size and vascularity, although the vascularity remained (arrow). (B) Chemotherapy for SCC of the oropharynx resulted in progressive disease. (C) HCC enlarged after administration of nivolumab (arrow).*

Discussion

We described the clinical courses of MPM patients after ICI administration. This is the first report of the effect of ICIs on patients with MPM, including HCC. The effect of atezolizumab on MPM has not been reported thus far.

MPM cases have been reported in the literature (6, 7). HCC reportedly had simultaneous or metachronous primary malignancies (7). The prevalence of gastric, head and neck, urinary tract, prostate, breast, and colorectal cancers was relatively higher than that of other malignancies with HCC in Japan (7). During the early stages, these malignancies can be treated with surgical resection or other locoregional therapies.

Advanced-stage tumors are treated with chemotherapy. Several first-line drugs have been recommended by guidelines for the treatment of different malignancies. However, the first-

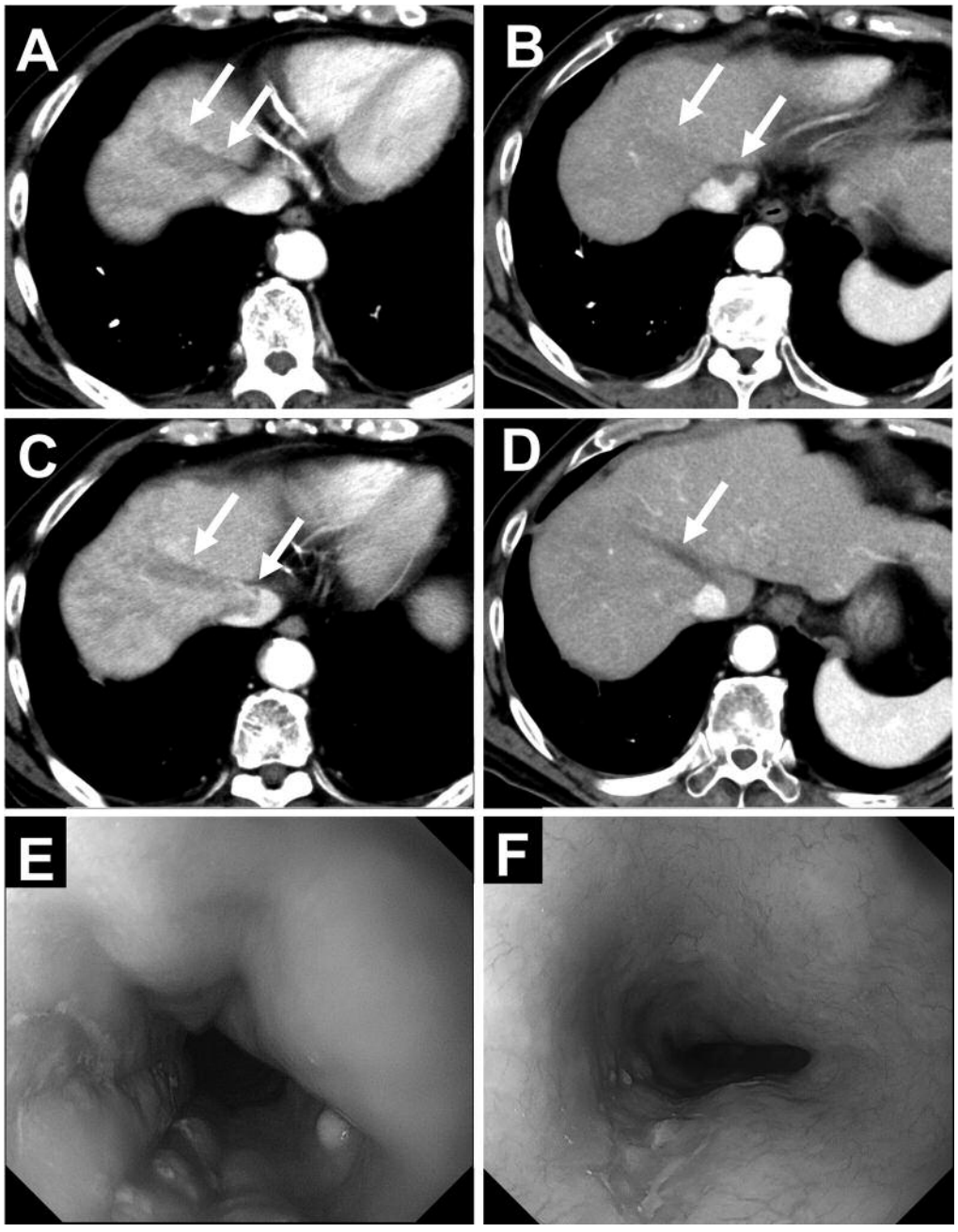

Figure 3. *Case 3. (A, B) The Contrast-enhanced CT revealed a 5-cm tumor in segment 4, invading the inferior vena cava through the right hepatic vein, with hyperenhancement in the arterial phase (arrow). (C, D) The contrast-enhanced CT after two months showed a partial response (arrow). (E) EGD revealed a shallow depressed lesion in the upper esophagus. (F) EGD at seven months after the initiation of chemotherapy showed slight improvement.*

line drugs for MPM have not been determined because of the diverse combinations of malignancies.

Conventional cytocidal anticancer drugs or molecular targeted agents (MTAs) can be used for a limited number of malignancies. In contrast, ICI influences a patient's immune system. Therefore, it can be effective for various malignancies. A small number of patients with MPM have been treated with ICIs (9-17) (Table II). In some cases, both malignancies significantly responded to ICI therapy (9-12). In other cases, the malignancies responded variably to ICI therapy (14-16).

Table I. *Profile of presented cases*.

Case	Age	Gender	1st primary cancer	2nd primary cancer	BCLC stage	Drug	Maximum efficacy of SCC	Maximum efficacy of HCC	Outcome
1	70	Male	Lung cancer	HCC	B	Nivolumab	SD	SD	21M, alive
2	58	Male	Oropharynx cancer	HCC	C	Nivolumab	PD	PD	15M, death
3	71	Male	HCC	Esophageal cancer	C	Atezolizumab and Bevacizumab	SD	PR	9M, alive

BCLC: The Barcelona Clinic Liver Cancer; SCC: squamous cell carcinoma; HCC: hepatocellular carcinoma; SD: stable disease; N/A: not available; PR: partial response.

Table II. *Review of previous literature of ICI for MPM*.

No.	Author	Year	Age	Gender	1st primary cancer	2nd primary cancer	Drug	Maximum efficacy of 1st cancer	Maximum efficacy of 2nd cancer	Outcome
12	Dhandha	2012	N/A	Female	Melanoma	RCC	Ipilimumab	PD	PD	N/A
9	Yamasaki	2017	76	Male	Lung cancer	Gastric cancer	Nivolumab	PR	PR	3M, alive
10	Hauschild	2017	51	Male	Melanoma	Non-melanoma skin cancer	Pembrolizumab	CR	CR	8M, alive
13	Yamaguchi	2017	63	Male	Lung cancer (NSCLC)	Hypopharyngeal cancer	Nivolumab	SD	PR	6M, alive
14	Arenbergerova	2018	49	Male	CLL	Melanoma	Pembrolizumab	SD	CR	21M, alive
15	Nozawa	2018	70	Male	Colon cancer	Lung cancer (SCC)	Pembrolizumab	SD	PR	11M, alive
11	Musher	2019	55	Female	Colon cancer	Intrahepatic cholangiocarcinoma	Pembrolizumab	CR	CR	18M, alive
16	Yamada	2019	83	Male	Lung cancer (NSCLC)	Bladder cancer	Pembrolizumab	PR	SD	10M, alive
			78	Male	Gastric cancer	Lung cancer (NSCLC)	Pembrolizumab	CR	PR	3M, alive
17	Eglmeier	2020	79	N/A	CLL	Skin cancer (SCC)	Pembrolizumab	PD	PD	N/A
			71	N/A	CLL	Skin cancer (SCC)	Nivolumab	PD	PD	N/A

ICI: Immune checkpoint inhibitor; MPM: multiple primary malignancy; RCC: renal cell carcinoma; NSCLC: non-small cell lung cancer; CLL: chronic lymphocitic leukemia; SCC: squamous cell carcinoma; HCC: hepatocellular carcinoma; SD: stable disease; N/A: not available; PR: partial response.

The difference in responsiveness to ICI was likely due to the difference in PD-1 or PD-L1 expression (14).

In this report, two of the three patients with double cancer, including HCC, benefitted from ICI therapy (Table I). In case 1, both HCC and lung cancer stabilized for nine months. In case 3, the HCC partially responded, whereas the esophageal cancer stabilized. Unfortunately, genetic testing was not performed in these three cases. Investigating the expression of PD-1 or PD-L1 may predict the efficacy of ICI. Although the positive rate of PD-1 or PD-L1 expression is low in HCC (18), a regimen, consisting of ICI and another MTA, was reportedly efficacious against HCC (1). Based on the efficacy of ICI for various cancers, a regimen, including ICIs, may be recommended as the first-line therapy for synchronous MPM.

In conclusion, ICI had the potential to affect more than two cancer types. Thus, a combination therapy including ICI is a promising treatment option for HCC with concurrent malignancies.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Hiroshi Aoki: Paper writing; Naoki Matsumoto: Study concept, Paper writing; Kazushige Nirei, Hiroaki Yamagami: Data collection; Hiroshi Takahashi, Masayuki Honda, Tomohiro Kaneko, Shuhei Arima,

Tomotaka Ishii, Taku Mizutani, Ryota Masuzaki, Masahiro Ogawa, Tatsuo Kanda, Mitsuhiko Moriyama: Katsuhiro Miura: Supervision.

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