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【 CASE REPORT 】

Synchronous Primary Lung Adenocarcinoma and Hepatocellular Carcinoma Successfully Treated with a Combination of Atezolizumab, Bevacizumab, Carboplatin, and Paclitaxel

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Abstract:

Chemotherapy for multiple primary malignancies is challenging. We herein report a case of synchronous primary lung adenocarcinoma and hepatocellular carcinoma (HCC). A 72-year-old man was admitted for the evaluation of an abnormal shadow on his lung. Computed tomography revealed a lung nodule in the right upper lobe and multiple liver masses. He was diagnosed with synchronous primary lung adenocarcinoma and HCC. Atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) chemotherapy was efficacious for both tumors. ABCP chemotherapy may be a potential treatment option for synchronous primary lung adenocarcinoma and HCC.

Key words: multiple primary malignancies, lung cancer, hepatocellular carcinoma, atezolizumab, bevacizumab

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Introduction

Multiple primary malignancies (MPMs) are defined as the presence of two or more independent primary malignancies in the same or different organs in a patient (1). MPMs occurring simultaneously or within 6 months of each other are called "synchronous," otherwise they are called "metachronous" (2). The prevalence of MPMs has been reported to be 0.73-11.7%, with 30-40% of these being synchronous tumors (1, 3-5).

Treatment of synchronous MPMs is clinically difficult. For both cancers in such cases, surgery is the preferred treatment option if both tumors are resectable. However, systemic therapy is the main treatment for patients with metastatic disease. When considering chemotherapy for two synchronous cancers, the treatment strategy is challenging.

Immune checkpoint inhibitors have recently caused a paradigm shift in the treatment of various types of cancer. In non-small-cell lung cancer (NSCLC), a combination of an immune checkpoint inhibitor and cytotoxic chemotherapy was recently approved (6, 7). For patients with unresectable hepatocellular carcinoma (HCC), the efficacy of atezolizumab plus bevacizumab has been demonstrated to be superior to sorafenib (8). However, there is no established standard therapy for synchronous lung cancer and HCC.

We herein report a case of synchronous primary lung adenocarcinoma and HCC that responded well to atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) chemotherapy.

Case Report

A 72-year-old man with diabetes mellitus was referred to the respiratory clinic of our hospital for the examination of an abnormal shadow on his lung. He had smoked approxi-

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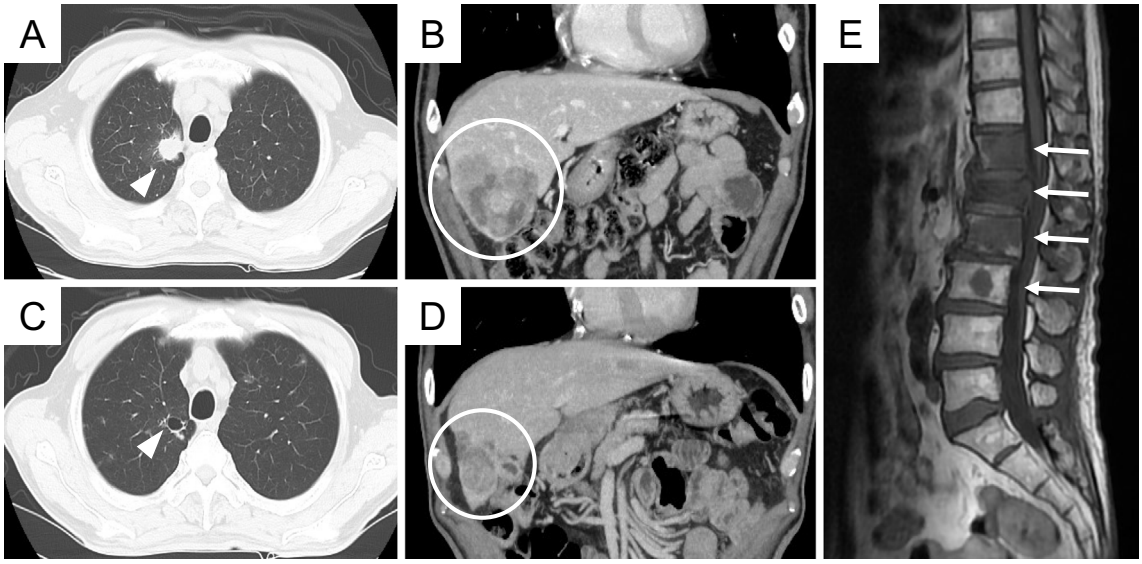

Figure 1. **CT findings of lung cancer (arrowhead; A, C) and HCC (circle; B, D) clinical course showed an isolated pulmonary nodule in the right upper lobe (A) and multiple liver masses (B). After four cycles of ABCP chemotherapy, the lung and liver tumors (C, D) decreased in size. Sagittal T2-weighted magnetic resonance imaging revealed bone metastases at the Th10 and L1 to L5 spinal levels. Vertebral lesions of Th12 to L3 are indicated (arrow; E). ABCP: atezolizumab, bevacizumab, carboplatin, and paclitaxel, CT: computed tomography, HCC: hepatocellular carcinoma, MRI: magnetic resonance imaging**

Table. **Laboratory Data on Admission.**

WBCs	6.08×10^3 /μL	BUN	18.4 mg/dL
RBCs	413×10^4 /μL	Cr	0.63 mg/dL
Hb	13.5 g/dL	HbA1c	6.6 %
Plt	22.0×10^4 U/L	CEA	16.7 ng/mL
PT	105.1 %	SLX	110 U/mL
TP	7.1 g/dL	AFP	517 ng/mL
Alb	4.2 g/dL	PIVKA-II	1,240 mAU/mL
T.bil	0.55 mg/dL	HBsAg	(-)
AST	33 μg/dL	HBsAb	(-)
ALT	15 U/L	HBcAb	(+)
LDH	211 U/L	HBV-DNA	ND
ALP	424 U/L	HCVAb	(-)
γ-GTP	78 U/L		

WBCs: white blood cells, RBCs: red blood cells, Hb: hemoglobin, Plt: platelets, TP: total protein, Alb: albumin, T.bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltranspeptodase, BUN: blood urine nitrogen, Cr: creatinine, HbA1c: hemoglobin A1c, CEA: carcinoembryonic antigen, SLX: sia-lyl Lewis X antigen, AFP: alpha fetoprotein, PIVKA-II: protein induced by vitamin K absence or antagonist-II, HBsAg: hepatitis B surface antigen, HBsAb: hepatitis B surface antibody, HBcAb: hepatitis B core antibody, ND: not detected, HCVAb: hepatitis C virus antibody

mately one pack of cigarettes per day for 51 years. He had been experiencing lower back pain for a month. The Eastern Cooperative Oncology Group performance status score of this patient was 1. Chest computed tomography (CT) showed a nodule with a maximum diameter of 18 mm in the right upper lung lobe (Fig. 1A), with lymph node swelling in the mediastinum. Abdominal CT demonstrated 2 mixed-density masses in the liver (72×65 mm and 15×13 mm) with enhancement during the arterial phase and washout during the venous phase (Fig. 1B). Magnetic resonance imaging revealed bone metastases at the Th12 to L3 spinal levels, including pathological fracture at the L1 spinal level (Fig. 1E).

Tumor marker tests revealed increased serum carcinoembryonic antigen (CEA) at 16.7 ng/mL, sialyl Lewis X at 110 U/mL, alpha-fetoprotein (AFP) at 517.4 ng/mL, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) at 1,240 ng/mL (Table). Serum hepatitis B core antibody was positive, whereas hepatitis B surface antigen and antibody were negative. HBV-DNA [Polymerase chain reaction (PCR)] was negative (Table). He did not have liver cirrhosis.

To differentiate synchronous double cancer from lung cancer with liver metastasis, we performed a transbronchial lung biopsy as well as a percutaneous liver biopsy. A histological examination of the lung biopsy specimen showed poorly differentiated lung adenocarcinoma immunopositive for thyroid transcription factor-1 (TTF-1) and immunonegative for p40 and hepatocyte paraffin 1 (Hep-par1) (Fig. 2A-C). The specimen was negative for epidermal growth factor receptor gene mutations, anaplastic lymphoma kinase, and c-ros oncogene 1 rearrangements. An immunohistochemical analysis of PD-L1 expression using the murine 22C-3 antibody revealed a tumor proportion score of more than 50%. Biopsy specimens obtained from the liver tumor revealed HCC corresponding to Edmondson-Steiner grade I (Fig. 2D). An immunohistochemistry analysis of the liver tumor showed cytoplasmic but not nuclear staining for

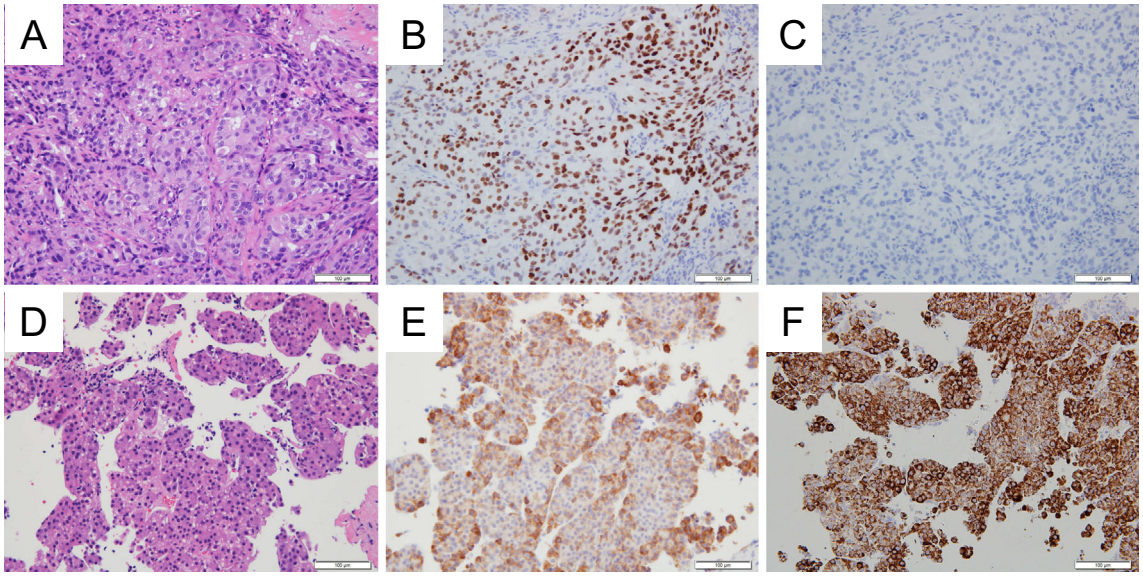

Figure 2. **Pathological findings of the pulmonary nodule (A-C) and liver mass (D-F). (A) The lung biopsy specimen is suggestive of poorly differentiated adenocarcinoma with solid nests of tumor cells, nuclear pleomorphism, and high nuclear/cytoplasmic (N/C) ratios [Hematoxylin and Eosin (H&E) staining; magnification, ×100]. (B) Tumor cells are immunopositive for TTF-1 (magnification, ×100). (C) Tumor cells are immunonegative for Hep-par 1 (magnification, ×100). (D) The ultrasound-guided, percutaneous liver biopsy specimen is suggestive of HCC with a thick trabecular/sinusoidal pattern (H&E staining; magnification, ×400). (E) Nuclei of tumor cells are immunonegative for TTF-1 (magnification, ×100). (F) Tumor cells are immunopositive for Hep-par 1 (magnification, ×100). HCC: hepatocellular carcinoma, Hep-par 1: hepatocyte paraffin 1, TTF-1: thyroid transcription factor-1**

TTF-1 and immunopositivity for Hep-par1 (Fig. 2E, F). We therefore diagnosed this patient with cT2N3M1c stage IVB lung adenocarcinoma (OSS) and cT3N0M0 stage III HCC.

ABCP chemotherapy was administered as the first-line treatment, with the inclusion of palliative radiation therapy for lumbar spinal metastases. These therapies resulted in an improvement in his back pain. The third and fourth treatment cycles were complicated by grade 3 nausea and decreased appetite. CT performed after 4 cycles of ABCP chemotherapy revealed the significant shrinkage of the tumors, with a 59.9% reduction in the lung adenocarcinoma and a 48.2% reduction in the HCC, which was evaluated as a partial response (Fig. 1C, D). His CEA and AFP tumor marker levels decreased to the normal range (Fig. 3). Following the completion of three cycles of continuous maintenance therapy with atezolizumab and bevacizumab, the size of the tumors continued to shrink without evidence of systemic progression or elevated levels of CEA and AFP.

Discussion

We encountered a patient with synchronous primary lung adenocarcinoma and HCC. Both tumors showed a good response to ABCP chemotherapy.

The incidence of MPMs has increased because the survival time of patients with cancer has increased with the development of new medical screening modalities and treatments. Lung cancer is one of the most frequent tumors encountered in synchronous MPM (9), and the most common accompanying tumors are gastrointestinal tumors (10, 11). Reports on synchronous MPMs of primary lung cancer and HCC are limited. In a previous study of 938 patients with NSCLC, only 5 patients had HCC (11). However, synchronous MPMs of primary lung cancer and HCC might be misdiagnosed as lung cancer with liver metastasis (12). In the present case, we suspected synchronous MPMs of primary lung cancer and HCC based on the increased serum AFP and PIVKA-II levels. Physicians should consider performing a biopsy of both tumors in such cases.

Based on histological and immunohistochemical analyses, we diagnosed this case as primary lung adenocarcinoma and synchronous HCC. TTF-1 is useful in the diagnosis of lung adenocarcinoma, as it appears as nuclear staining (13). HCC has been noted to be stained by TTF-1 in a cytoplasmic pattern (14). In the present case, TTF-1 was useful for discriminating between HCC and lung cancer with liver metastasis.

In the present case, synchronous primary lung adenocarcinoma and HCC tumors had decreased in size because of ABCP therapy. Recently, the combination of immunotherapy and chemotherapy has become the standard first-line therapy for patients with NSCLC without *EGFR* or *ALK* mutations (6, 7). Furthermore, the IMbrave150 trial showed that the combination of atezolizumab and bevacizumab achieved

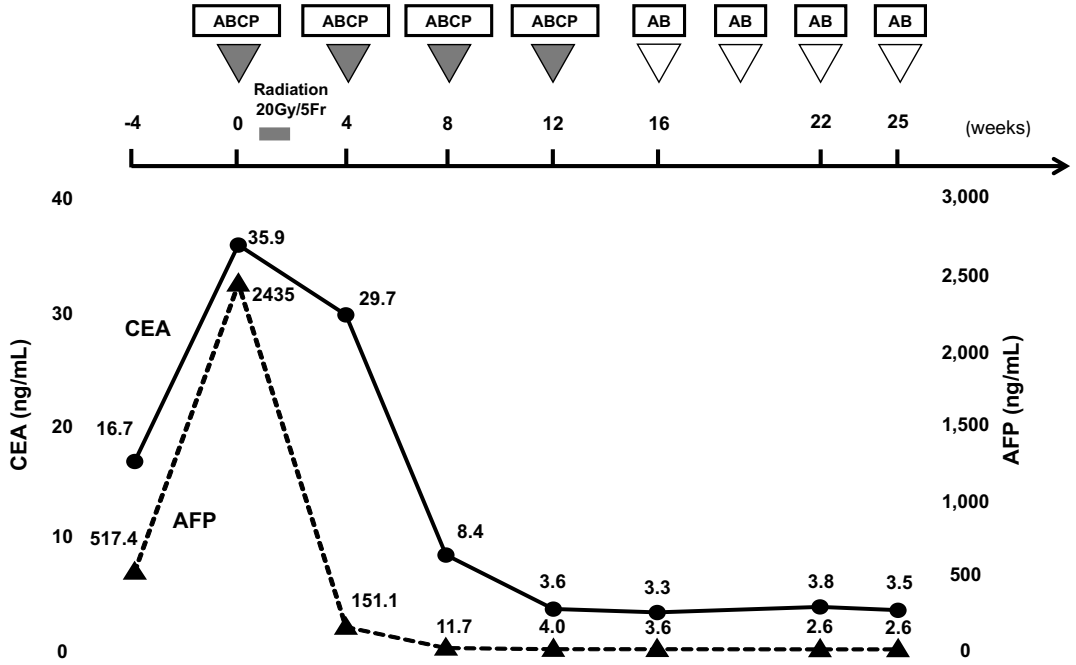

Figure 3. Treatment course, CEA, and AFP levels after the diagnosis of lung cancer and HCC. AB: atezolizumab and bevacizumab, ABCP: atezolizumab, bevacizumab, carboplatin, and paclitaxel, AFP: alpha-fetoprotein, CEA: carcinoembryonic antigen

better overall and progression-free survival rates than sorafenib in unresectable HCC (8).

Because the prognosis of the patient seemed to be defined by the metastatic lung adenocarcinoma rather than by HCC, combination treatment with immune checkpoint inhibitors and chemotherapeutic drugs for lung cancer was selected. Considering the effect on HCC, the ABCP regimen, including atezolizumab and bevacizumab rather than pemetrexed and pembrolizumab, seemed to be the best choice for the first-line treatment of the patient.

To our knowledge, this is the first report of a case of synchronous primary lung adenocarcinoma and HCC that showed a good response to ABCP chemotherapy. Thus, ABCP chemotherapy may be an effective option for the treatment of synchronous primary lung cancer and HCC.

The authors state that they have no Conflict of Interest (COI).

References

1. Irimie A, Achimas-Cadariu P, Burz C, Puscas E. Multiple primary malignancies--epidemiological analysis at a single tertiary institution. J Gastrointest Liver Dis **19**: 69-73, 2010.
2. Moertel CG, Dockerty MB, Baggenstoss AH. Multiple primary malignant neoplasms. I. Introduction and presentation of data. Cancer **14**: 221-230, 1961.
3. Hayat MJ, Howlader N, Reichman ME, et al. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist **12**: 20-37, 2007.
4. Aydiner A, Karadeniz A, Uygun K, et al. Multiple primary neoplasms at a single institution: differences between synchronous and metachronous neoplasms. Am J Clin Oncol **23**: 364-370, 2000.
5. Liu Z, Liu C, Guo W, Li S, Bai O. Clinical analysis of 152 cases of multiple primary malignant tumors in 15,398 patients with malignant tumors. PLoS One **10**: e0125754, 2015.
6. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med **378**: 2078-2092, 2018.
7. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med **378**: 2288-2301, 2018.
8. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med **382**: 1894-1905, 2020.
9. Komatsu H, Izumi N, Tsukioka T, et al. Prognosis associated with synchronous or metachronous multiple primary malignancies in patients with completely resected non-small cell lung cancer. Surg Today **49**: 343-349, 2019.
10. Fujita S, Masago K, Takeshita J, et al. Multiple primary malignancies in patients with non-small cell lung cancer. Intern Med **54**: 325-331, 2015.
11. Aydiner A, Karadeniz A, Uygun K, et al. Multiple primary neoplasms at a single institution: differences between synchronous and metachronous neoplasms. Am J Clin Oncol **23**: 364-370, 2000.
12. Zhang M, Kong F, Liu Y, et al. Case report synchronous primary lung cancer and hepatic cancer versus hepatic metastasis: a report of three cases and literature review. Int J Clin Exp Med **10**: 16721-16726, 2017.
13. Ordonez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. Adv Anat Pathol **7**: 123-127, 2000.
14. Wieczorek TJ, Pinkus JL, Glickman JN, Pinkus GS. Comparison of thyroid transcription factor-1 and hepatocyte antigen immunohistochemical analysis in the differential diagnosis of hepatocellular carcinoma, metastatic adenocarcinoma, renal cell carcinoma, and adrenal cortical carcinoma. Am J Clin Pathol **118**: 911-921, 2002.