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Letter to the Editor

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Immune Checkpoint Inhibitor-Related Pneumonia in Unresectable Hepatocellular Carcinoma: Two Fatal Cases under Atezolizumab plus Bevacizumab

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Dear Editor,

We read with interest a recent study published in the journal by Ng et al. [1], regarding the positive relationship observed between immune-related adverse events (irAE) and the clinical outcomes in patients with advanced hepatocellular carcinoma (HCC) treated with immune checkpoint inhibitors (ICI). However, irAE can sometimes be lethal and therefore requires a high degree of caution.

The recent updated IMbrave150 trial reported that patients with treatment-related pneumonia accounted for approximately 1% of the patients, including one who died due to an adverse event [2]. ICI-related pneumonia is a rare but potentially life-threatening irAE. Indeed, ICI-related pneumonia is the most common fatal irAE in patients with cancers other than HCC who receive programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors, accounting for 35% of PD-1/PD-L1 inhibitor-related deaths [3]. We herein report 2 fatal cases involving patients treated with atezolizumab plus bevacizumab for HCC. In both patients, ICI-related pneumonia was provisionally the cause of death.

Case 1 was an 85-year-old woman with hepatitis B, who developed HCC 6 years previously. After 5 transcatheter arterial chemoembolization treatments, she was treated by systemic chemotherapy with sorafenib for 5 months and ramucirumab for the subsequent 4 months. Chest CT showed honeycomb lung in the lower lobes before treatment (Fig. 1a). Abdominal CT showed multiple intrahepatic recurrences. Since her liver function was well preserved (Child-Pugh class A), we started to treat the patients with intravenous atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) every 3 weeks. She complained of grade 1 cough (CTCAE ver 5.0) on day 5 after the start of ICI therapy and was admitted to our hospital on day 18 because of anorexia, malaise, and dyspnea. Chest CT showed bilateral interstitial pneumonia (Fig. 1b). The patient was judged to have grade 3 ICI-related pneumonia because other causes of dyspnea (e.g., respiratory infection and cardiac disease) were denied. Since the patient did not respond to intravenous prednisolone (1 mg/kg) within 48 h, we treated her with steroid pulse therapy (methylprednisolone, 1,000 mg/day) for 3 days, followed by prednisolone (1.5 mg/kg). The serum KL-6 level was 381 U/mL (normal <500 U/mL) before treatment, 421 U/mL at admission, and 1,523 U/mL 7 days after admission. However, she died of respiratory failure on the 29th day after the start of ICI treatment. Autopsy revealed diffuse

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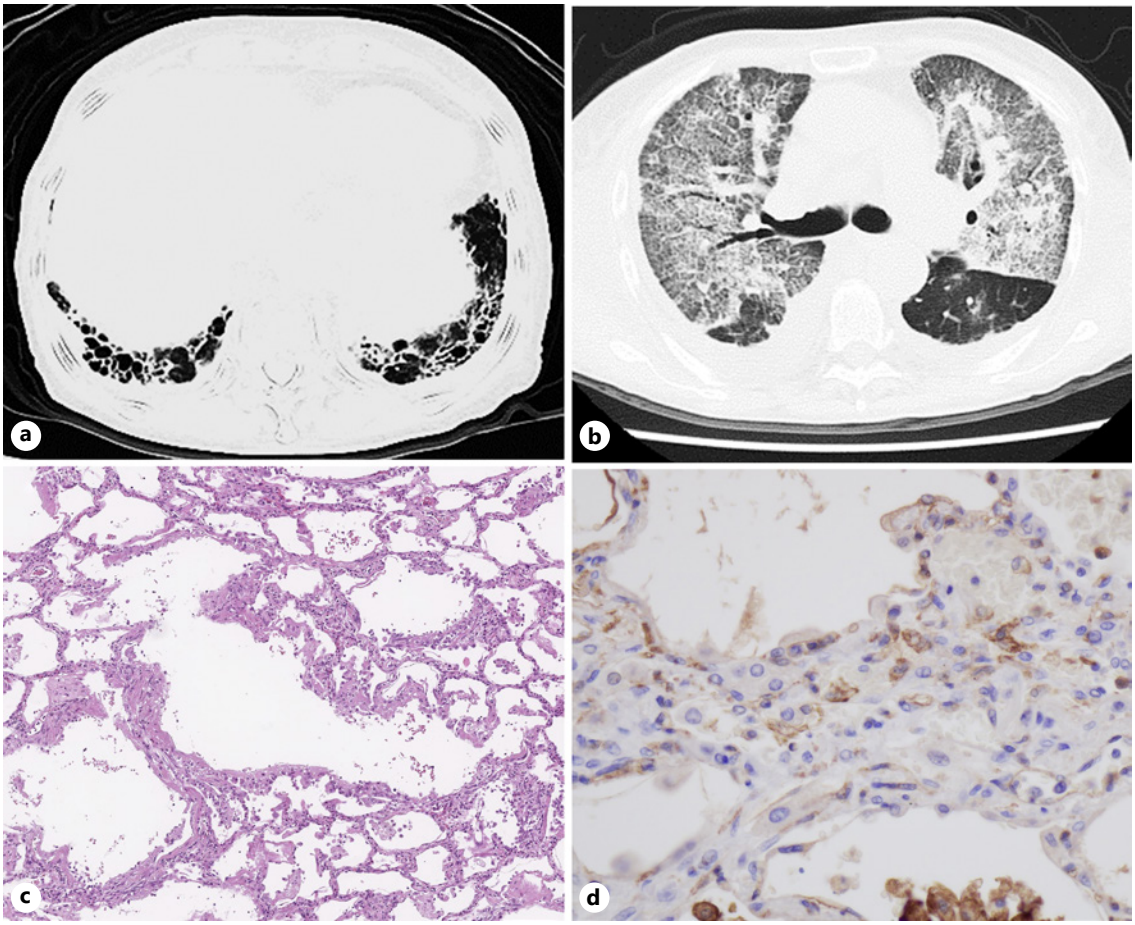

Fig. 1. Clinical images and pathological findings of case 1. **a** Chest CT showed a honeycomb lung in the lower lobe of the lung before atezolizumab plus bevacizumab treatment. **b** CT findings after 18 days of atezolizumab plus bevacizumab treatment showed ground-glass opacity with consolidations and traction bronchiectasis in both lungs. **c** Microscopic findings of the lung revealed hyaline membrane formation in the alveoli, indicating the exudative phase of diffuse alveolar damage. **d** Immunohistochemical studies showed many PD-L1-positive cells in mesenchymal tissue (×400).

alveolar damage in the upper and middle lobes of both lungs (Fig. 1c) and honeycomb lung in the lower lobe. These findings suggested chronologically different phases of inflammation. Mild infiltration of CD4- and CD8-positive lymphocytes was present, together with prominent PD-L1-positive cells in the mesenchymal tissue of the lung (Fig. 1d).

Case 2 was an 88-year-old woman who developed HCC associated with type C cirrhosis. She underwent laparoscopic hepatic resection of segment 6, 2 radiofrequency ablation treatments, and 2 transcatheter arterial chemoembolization treatments. She had undergone thoracoscopic right lower lobectomy for lung adenocarcinoma 6 years previously without a subsequent recurrence. Abdominal CT showed multiple intrahepatic and extrahepatic recurrences (Fig. 2a). Since her liver function was well preserved (Child-Pugh class A), the patient was treated with atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) every 3 weeks. After 5 courses of ICI treatment, bevacizumab was discontinued due to grade 3 proteinuria, while atezolizumab was sustained. Abdominal plain CT showed a partial response of the extrahepatic lesions (Fig. 2b). After 11 courses of treatment, however, the patient was hospitalized for dyspnea. Chest CT showed bilateral interstitial pneumonia (Fig. 2c), which was diagnosed as ICI-related pneumonia. The serum KL-6 levels were 360 U/mL before ATZ + BEV administration, 486 U/mL after 10 courses, and 819 U/mL at admission. She did not respond to steroid treatment and died on the 6th day of hospitalization.

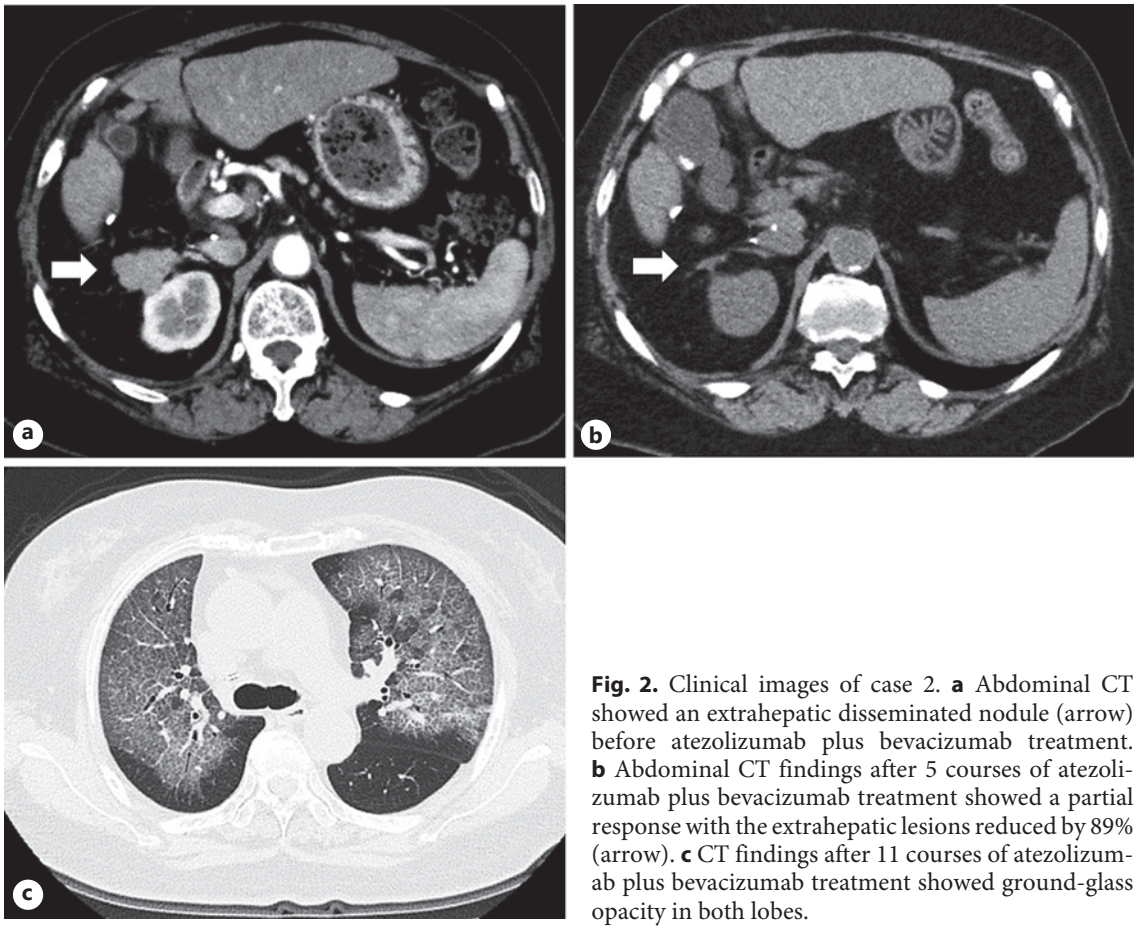

Fig. 2. Clinical images of case 2. **a** Abdominal CT showed an extrahepatic disseminated nodule (arrow) before atezolizumab plus bevacizumab treatment. **b** Abdominal CT findings after 5 courses of atezolizumab plus bevacizumab treatment showed a partial response with the extrahepatic lesions reduced by 89% (arrow). **c** CT findings after 11 courses of atezolizumab plus bevacizumab treatment showed ground-glass opacity in both lobes.

Discussion

A recent study on the ICI therapy for lung cancer reported that the presence of pulmonary fibrosis before treatment is a risk factor for the development of ICI-related pneumonia [4]. Moreover, a phase 2 study of atezolizumab for non-small cell lung cancer with pre-existing interstitial pneumonia was terminated early due to the high incidence of ICI-related pneumonia [5]. As was confirmed in those clinical trials, our two cases of ICI-related pneumonia were characterized by a history of lung disease. Indeed, case 1 had preceding interstitial pneumonia and developed ICI-related pneumonia immediately after the start of ICI therapy. Case 1 was treated with ATZ + BEV after consultation with a pulmonologist prior to treatment. The decision was made because the patient did not respond to standard first- and second-line chemotherapy and was determined to have inactive interstitial lung disease based on the absence of respiratory symptoms and elevated KL-6 levels. The concentration of serum KL-6, a known biomarker for interstitial lung disease, was elevated after the onset of ICI-related pneumonia but was not predictive of the onset of ICI-related pneumonia in our cases. Thus, special attention to preceding interstitial lung damage seems inevitable when ICIs have become the choice of treatment, even for HCC patients.

We found that the lung damage in case 1 was characterized by the infiltration of PD-L1-positive cells. This strongly suggests that ICI-related pneumonia is predominantly a consequence of an increased immune response via the breakdown of the PD-1/PD-L1 system. In conclusion, our experiences suggest the need for careful monitoring of ICI-related pneumonia in HCC patients, particularly those with pre-existing lung disease.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Kei Endo: study concept and design and drafting of the manuscript. Hidekatsu Kuroda: acquisition of data and critical revision of the manuscript for important intellectual content. Takayoshi Oikawa, Tamami Abe, Youhei Kooka, Keisuke Kakisaka, and Akio Miyasaka: acquisition of data. Yuma Ito and Tamotsu Sugai: pathological assessment. Takayuki Matsumoto: critical revision of the manuscript for important intellectual content and study supervision.

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