A case of hyperprogressive disease following atezolizumab therapy for pulmonary pleomorphic carcinoma with epidermal growth factor receptor mutation

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ABSTRACT

A 66-year old man with non-smoking history was diagnosed with pulmonary pleomorphic carcinoma of the right lower lobe. The carcinoma metastasized to the brain, lungs, pleura, and mediastinal lymph nodes. It was positive for *epidermal growth factor receptor (EGFR)* L858R mutation, and tumor cells highly expressed programmed death-ligand 1(PD-L1). Atezolizumab was initiated as the fourth treatment. After three days, he developed cardiac tamponade and immediately underwent pericardial drainage. Computed tomography showed bilateral ground-glass opacity (GGO), significant worsening of multiple lung metastases, and increased size of metastatic lesions. Newly developed metastasis was noted in the lung, and the patient's respiratory condition rapidly deteriorated. He died of respiratory failure on day 13 after atezolizumab administration. The autopsy showed widespread metastasis in all lobes of the bilateral lungs, cardiac tamponade due to carcinomatous pericarditis, carcinomatous lymphangiopathy, and multiple lung metastases, which were thought to be comprehensively the cause of death. These symptoms suggested hyperprogressive disease (HPD). Hence, we report the first case of HPD following atezolizumab therapy for pulmonary pleomorphic carcinoma with *EGFR* mutation.

1. Introduction

Atezolizumab is a humanized anti-programmed death-ligand 1 (PD-L1) monoclonal antibody that inhibits PD-L1 and programmed death-1 (PD-1) as well as interactions between PD-L1 and B7-1. It functions as an immune checkpoint inhibitor (ICI) and is used to treat metastatic lung cancer [1]. Although, ICIs are shown to be effective for a variety of carcinoma including non-small cell lung carcinoma (NSCLC) [1], there have also been cases of rapid progression, a condition called hyperprogressive disease (HPD). While several hypotheses on HPD have been proposed [2,3], its mechanism remains poorly understood. Herein, we report a case of HPD following atezolizumab therapy for pulmonary pleomorphic carcinoma with an epidermal growth factor receptor

mutation (*EGFR*).

1.1. Case report

A 66-year old man with a non-smoking history was diagnosed with pulmonary pleomorphic carcinoma of the right lower lobe with metastasis to the brain, lungs, pleura, and mediastinal lymph nodes. Next-generation sequencing (NGS) analysis of the sample taken by bronchoscopy from primary lesion showed mutations in the epidermal growth factor receptor (*EGFR*) L858R in exon 21, and R175H mutation in *TP53*. Immunohistochemistry (IHC) showed that PD-L1 expression on 90% positive of tumor cells. He did not respond to treatments with afatinib and osimertinib. However, he transiently responded to four
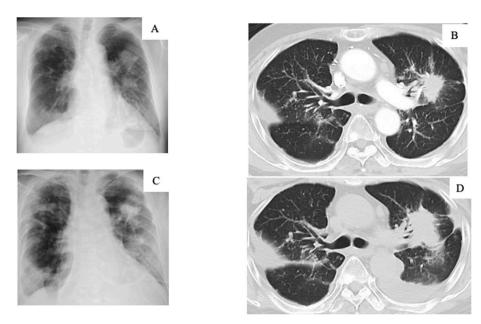

Fig. 1. Chest radiography and computed tomography (CT) (Fig. 1 A, B) revealed no pleural effusion and cardiac enlargement. Three days after administration of atezolizumab, chest radiography revealed cardiac enlargement (Fig. 1C). CT revealed increased sizes of old lesions, bilateral ground-glass opacity, and left pleural effusion (Fig. 1D).
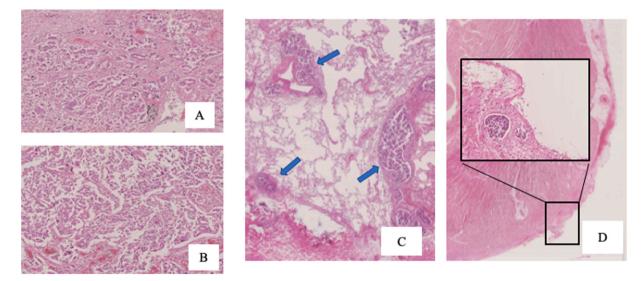

Fig. 2. Histopathological findings on autopsy.
Primary lesion shows pulmonary pleomorphic carcinoma including.
(A) micropapillary adenocarcinoma and
(B) spindle cell carcinoma.
(C) Lymphatic vessels are filled with cancer cells; the image shows findings of cancerous lymphangiopathy (blue arrows).
(D) The pericardium has mild infiltration of inflammatory cells, and lymphatic vessels are filled with cancer cells.

cycles (best-effect, partial response) of carboplatin and pemetrexed treatment but eventually developed PD. He then underwent talc pleurodesis for right-sided malignant pleural effusion and whole-brain radiation (30 Gy/10 Fr) for multiple brain metastases.

At our hospital, he was administered with atezolizumab [1] as the fourth line treatment. On admission, his vital signs were as follows: body temperature, 36.7 °C; blood pressure, 127/81 mmHg; heart rate, 96/min; respiratory rate, 12/min; oxygen saturation, 96% (room air); and performance status, 1. Owing to pleurodesis, left breath sounds were slightly attenuated. High levels of LDH (391 U/L; normal range, 120–220) and CEA (101.9; <0.5 ng/mL) were found. Chest radiography and computed tomography (CT) (Fig. 1 A, B) revealed no pleural

effusion and cardiac enlargement. Additionally, UCG showed no major abnormalities other than a small amount of pericardial fluid (0.3 cm).

After three days, he developed tachycardia, hypotension. He experienced dyspnea and required O_2 inhalation (SpO_2 96%; nasal 3L/min). X-ray examination showed mild cardiac enlargement and echocardiography showed a marked accumulation of pericardial effusion (2.7 cm). The patient was diagnosed with cardiac tamponade, and pericardial drainage was immediately performed. A large number of adenocarcinoma cells and no lymphocytes were seen in pericardial effusion cytology. After pericardial drainage, chest radiography revealed cardiac enlargement (Fig. 1C). A repeated CT of the chest revealed increased sizes of old lesions, bilateral ground-glass opacity, and left pleural

effusion (Fig. 1D). The patient's respiratory condition rapidly deteriorated (reservoir mask O$_2$ 6L; SpO$_2$ 92%) and LDH levels increased (706 U/L). On day 8, methylprednisolone (1 mg/kg) was administered [4] because drug-induced pneumonia related to immune-related adverse events (irAE) was suspected. The patient died of respiratory failure on day 13 after atezolizumab administration.

Autopsy showed widespread metastasis in all lobes of the bilateral lungs, cardiac tamponade due to carcinomatous pericarditis, carcinomatous lymphangiopathy, and exacerbation of multiple lung metastases (Fig. 2A-D), which were thought to be the cause of death. Autopsy revealed new metastases in the liver and diaphragm, bilateral pleural effusion, and pericardial fluid. Infiltration of lymphocyte-based inflammatory cells into the pericardium and lung field was mild, and there was no strong evidence suggestive of irAE. Thus, HPD was considered for diagnosis.

2. Discussion

Although, HPD in NSCLC due to atezolizumab has been reported [5] to the best of our knowledge, this is the first case report of atezolizumab-induced HPD involving pulmonary pleomorphic carcinoma with *EGFR* mutation.

The concept of HPD was first reported in retrospective studies of patients treated with ICIs based on clinical observations of patients whose diseases progressed faster after the initiation of immunotherapy [6–8]. They noted that 4–29% of HPD patients were treated with ICI [6, 9]. Based on previous studies, HPD was defined using the following criteria: (i) time-to-treatment failure <2 months (with treatment failure defined as ICI discontinuation due to cancer progression, drug toxicity, or death); (ii) a 50% increase in the sum of target lesion diameters between baseline and the first radiologic evaluation; (iii) development of at least two lesions in an already involved organ between baseline and the first radiologic evaluation; (iv) appearance of a new organ lesion between baseline and the first radiologic evaluation; and (v) a decrease in Eastern Cooperative Oncology Group Performance Status 2 during the first two months of treatment [10]. In this case, HPD was diagnosed because it satisfied four of these criteria.

In addition, HPD was associated with *MDM2/MDM4* amplification and *EGFR* alterations [11,12]. *MDM2* inhibits the tumor suppressor, p53 (MDM4 is a homolog of MDM2 that interacts with p53 and also inhibits it) [13]. Also, Hugo et al. was reported that it is associated HPD with BRCA2 mutations, conversely. In this case, NGS analysis of the primary lesion via bronchoscopy showed an epidermal growth factor receptor (*EGFR*) mutation L858R in exon 21 and R175H mutation in *TP53* mutation, but it did not have a BRCA2 mutation.

The therapeutic efficacy of atezolizumab is greater in tumor cells with higher degrees of PD-L1 expression [1,14]. However, HPD occurred in this case despite the high expression of PD-L1.

Kleffel et al. recently showed that PD-1/PD-ligand 1 (PD-L1) signaling had cell-intrinsic functions in certain types of mouse and human tumors, boosting cancer growth, and promoting tumorigenesis [15]. According to Kamada et al., tumors of HPD patients after treatment possessed highly proliferating FoxP3$^+$ Treg cells. HPD may occur when the PD-1 blockade activates and expands the tumor-infiltrating PD-1+ Treg cells to overcome the tumor-reactive PD-1+ effector T cells [3]. In the present case, autopsy revealed massive metastasis in the lungs, multiple organs, and pericardium with little lymphocytic infiltration. Therefore, we could not confirm the presence of FOXP3$^+$ Treg cells.

Despite the existence of several hypothesis of HPD [2,3], the mechanism of HPD is currently poorly understood.

Pulmonary pleomorphic carcinoma is rare, and its incidence ranges from 0.1% to 0.4% in all lung cancers [16]. It has an aggressive clinical course compared to other NSCLC, and the response to systemic chemotherapy is generally poor. There have been some reports of successful treatment of pleomorphic carcinoma with ICIs. However, *EGFR* mutations in pulmonary pleomorphic carcinoma are rarely detected [17], and the effect of ICI on pulmonary pleomorphic carcinoma with *EGFR* mutations is unclear.

The results of the CHANCE trial regarding antitumor activity of atezolizumab in advanced NSCLC patients with rare histology subtypes including pleomorphic carcinoma are not yet available [18].

Patients with HPD are reported to have a shorter overall survival [5], and the patient in the present case had an extremely short prognosis.

The presence of clinical risk factors for HPD still remains controversial. Choi et al. reported that the risk factors of HPD were age, primary lesion size, and metastases in the contralateral lung, pleura, liver, and bone [19]. However, Ferrara et al. and Kanjanapan et al. did not find any significant association between HPD and age [9,20]. In addition, a recent meta-analysis reported that age >65 years was not correlated with the development of HPD [17], and Champiat et al. reported that patients with HPD were older than those without HPD [6].

3. Conclusion

This is the first case report of HPD following atezolizumab therapy for pulmonary pleomorphic carcinoma involving *EGFR* mutation. HPD may occur earlier, as seen in this case, and attention should be paid to HPD when using ICIs in pleomorphic and *EGFR* mutation-positive cases. Biomarkers that could predict HPD reliably are needed to prevent the fatal condition.

Ethical statement

Appropriate written informed consent was obtained for the publication of this case report and accompanying images.

Declaration of competing interest

The authors declare that there is no conflict of interests regarding the publication of this article.

Acknowledgments

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