



Case report

Hyperprogressive disease after treatment with pembrolizumab in lung adenocarcinoma: An autopsy case study



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ARTICLE INFO

Keywords:

Hyperprogressive disease
Immune checkpoint inhibitors
Non-small cell lung cancer
PD-L1

ABSTRACT

Although immune-checkpoint inhibitors (ICIs) have become an important choice of treatment for advanced NSCLC, recent reports show hyperprogressive disease (HPD) after ICI administration. The clinico-pathological features of HPD still remain unclear. Here we report a 65-year-old man with lung adenocarcinoma who abruptly presented HPD two days after pembrolizumab administration. The primary tumor increased in size from 40 mm to 57 mm on the chest HRCT. The patient died on day 37 after pembrolizumab administration. The autopsy demonstrated widespread progression of cancer cells into the alveolar spaces and lymphangitic carcinomatosis in the left lung, with plenty of bloody pleural effusion. We compared the pathohistology and immunohistochemical expression of PD-L1 between the pretreatment biopsy material and posttreatment autopsy materials, and found a change in PD-L1 expression which may be related to HPD. We also discuss the possibility of HPD, pseudoprogession, and interstitial lung disease when there is evidence of tumor growth or ground glass shadows on chest images after ICI treatment.

1. Introduction

Recent work has shown that using immune-checkpoint inhibitors (ICIs) to treat NSCLC can cause hyperprogressive disease (HPD) [1–3], which is defined as accelerated tumor growth during ICI treatment [1–5]. HPD frequency in NSCLC has been reported to be as high as 8%–14% [3,5]. However, pseudoprogession which is not genuine tumor progression but initial radiographic progression from immune cell infiltration around tumors [4,5], and interstitial lung disease (ILD), a known adverse effect of ICIs [6], have been known for long as the complications of ICI administration. Therefore, when pulmonary lesions worsen during ICIs treatment in NSCLC, the differential diagnosis should consider HPD, pseudoprogession, and ILD. However, HPD's risk factors and mechanism remain unknown [1–5].

Here we present an autopsy case in which pulmonary lesions were enlarged after administration of pembrolizumab for NSCLC. We diagnosed HPD from clinical features and pulmonary pathology on autopsy.

2. Case presentation

A 65-year-old man presented to our hospital with a cough. The patient was a current smoker. High resolution computed tomography (HRCT) revealed a 28 mm mass shadow in the left lower lobe and enlargement of left hilar, mediastinal, and right subclavian lymph nodes (Fig. 1A). EBUS-TBNA biopsy was performed on the subcarinal lymph node. The patient was diagnosed with left lower lobe lung adenocarcinoma with cT3N3M0 and stage IIIB. Cancer cells showed EGFR wild type and were negative for anaplastic lymphoma kinase (ALK). Immunohistochemical expression of PD-L1 in the EBUS-TBNA biopsy was 98% (Fig. 2A and B). The patient had bilateral deep vein thrombosis (DVT) of the lower limbs and pulmonary microembolism, but he did not show exertional dyspnea and status 0 according to the ECOG Performance Status. The tumor shadow was 40 mm in the largest diameter on chest HRCT performed on the day before pembrolizumab treatment (Fig. 1B). Pembrolizumab (200 mg IV over 30 min) was initiated 22 days after the first visit. The patient's pulse oxygenation on

Abbreviations: ALK, anaplastic lymphoma kinase; EBUS-TBNA, Endobronchial ultrasound-transbronchial needle aspiration; DIC, Disseminated intravascular coagulation; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HPD, hyperprogressive disease; HRCT, high-resolution computed tomography; ILD, Interstitial lung disease; NSCLC, non-small cell lung cancer; PD-L1, Programmed cell death ligand 1

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<https://doi.org/10.1016/j.rmcr.2019.100885>

Received 5 March 2019; Received in revised form 12 June 2019; Accepted 12 June 2019

Available online 13 June 2019

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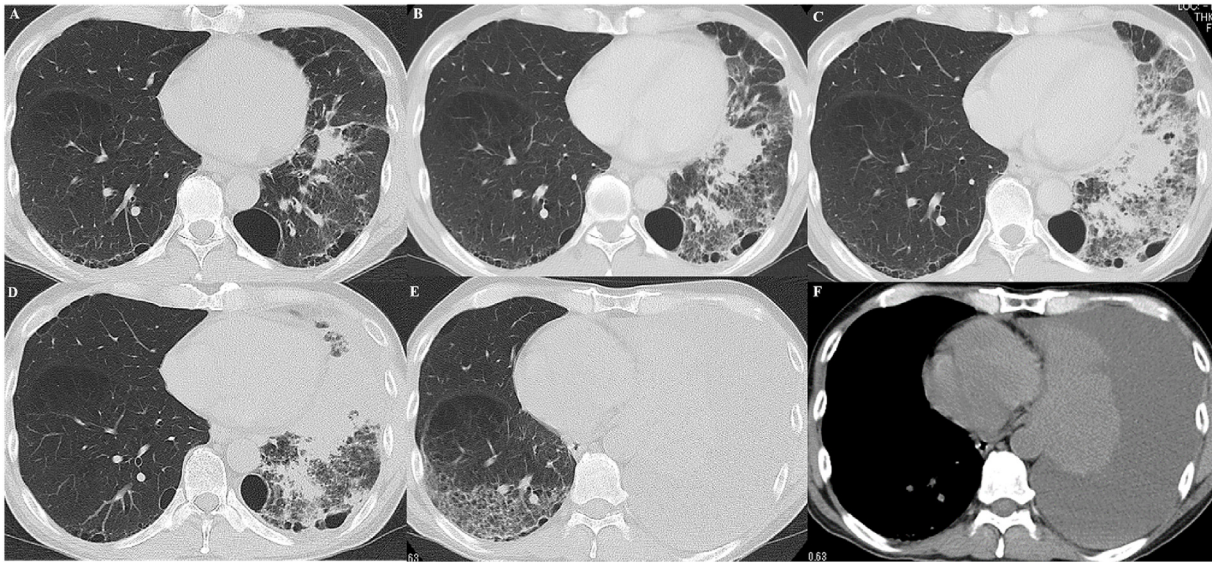


Fig. 1. HRCT images on the first visit revealed a 28-mm tumor in the left lower lobe (A). The tumor's long axis increased to 40 mm 21 days later (B). The tumor's long axis increased to 57 mm 24 days later (2 days after the initiation of pembrolizumab) (C). The tumor's long axis increased to 80 mm 43 days later (21 days after the initiation of pembrolizumab) (D). A large amount of bloody pleural effusion appeared 56 days later (34 days after initiation of pembrolizumab) (E, F).

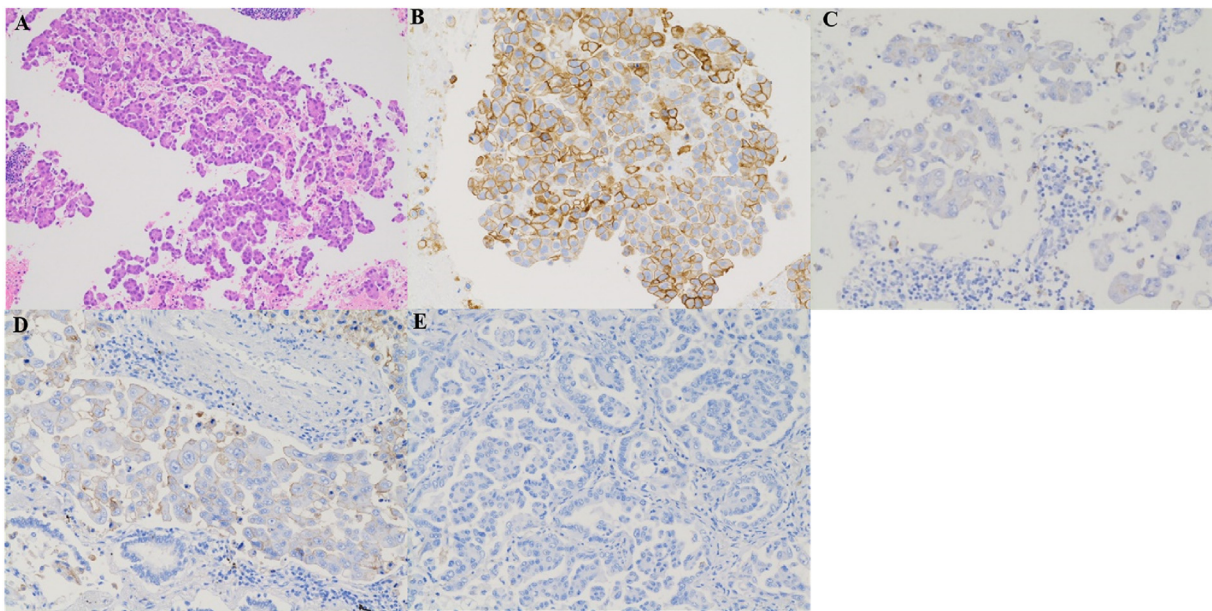


Fig. 2. Assessment of the subcarinal lymph node specimen by EBUS-TBNA (A) revealed that the PD-L1 expression rate was 98% before pembrolizumab administration (B) and less than 1% in the autopsy (C). The PD-L1 expression rate was different in the portions of the primary lung cancer at autopsy; the highest rate was 10% (D) and the lowest rate was less than 1% (E). The overall primary tumor expression rate was approximately 1% based on autopsy results. Original magnification: (A), (B), (D), (E) $\times 200$, (C) $\times 100$. Hematoxylin and eosin staining (A). PD-L1 expression was measured using a prototype immunohistochemistry assay with an anti-PD-L1 22C3 antibody (B)–(E).

room air worsened from SpO₂ 98%–90% two days after pembrolizumab administration. On chest HRCT, the primary tumor shadow increased in size to 57 mm, with growing of ground glass shadows (Fig. 1C). Serum KL-6 and lactate dehydrogenase (LDH) levels did not increase. Antibiotics were initiated as we suspected bacterial pneumonia; however, respiratory failure worsened on day 6 after pembrolizumab administration. We suspected interstitial lung disease (ILD) caused by pembrolizumab and started steroid pulse therapy. The ground glass shadow around the tumor improved, but the primary tumor increased in size to 80 mm on chest HRCT on day 21 after pembrolizumab administration (Fig. 1D). SpO₂ decreased to 93% (supplementary oxygen mask 4L) on day 21 after pembrolizumab administration. Serum tumor markers

were elevated, and the lung cancer progressed very rapidly with a complication of disseminated intravascular coagulation (DIC). Pembrolizumab treatment appeared ineffective; thus, we initiated carboplatin and nanoparticle paclitaxel administration. After the unexpected appearance of significant bloody pleural effusion (Fig. 1E and F), the patient died on day 37 after pembrolizumab administration.

Autopsy was performed 8.5 hours after death which confirmed that the primary tumor of the left lung was in the hilar part of the left lower lobe. Sections showed white, firm, and solid tumor masses in the hilar part of S8 and 9 and almost the entirety of left S4 and S5. Marked thickening of the bronchial wall of the hilar region was observed in the left B8-9 and B4-5, but there was no lumen obstruction. The

lymphangitic carcinomatosis was remarkable around the tumor mass and was widespread in the entire left lung. Lymphatic metastasis was observed in the left hilar, para-tracheal, mediastinal, and bilateral cervical lymph nodes. Fresh thromboemboli were found in the main pulmonary artery of the right lower lobe, and there were fresh and organized long thrombi in the right or left femoral veins, which were suspected to be the origin of the pulmonary artery thromboembolism. The lung cancer histology was aggressive mucinous adenocarcinoma and the predominant cancer histology was micropapillary pattern. Widespread alveolar spaces were filled up with cancer cells in the left upper and lower lobes. Histological examination demonstrated lymphangitic carcinomatosis, tumor thrombi in the small pulmonary veins. At autopsy, the bleeding source of left bloody pleural effusion could not be identified. It is thought that the strong lung congestion, dissemination of lung cancer that was found throughout the left pleura, and that bleeding tendency due to DIC were involved. We determined the cause of death to be respiratory failure due to widespread infiltration of lung cancer, which was brought about by HPD after pembrolizumab treatment.

We compared the PD-L1 expression rate of the cancer tissue in the subcarinal lymph node, taken by EBUS-TBNA biopsy (Fig. 2A), to the identical lymph node taken at autopsy. It was 98% in the EBUS-TBNA (Fig. 2B) and less than 1% in the autopsy (Fig. 2C). The PD-L1 expression rate was different in the portions of the primary lung cancer at autopsy, with the highest rate at 10% (Fig. 2D) and the lowest < 1% (Fig. 2E). The overall expression rate of the primary tumor at autopsy was approximately 1%. A primary tumor specimen before pembrolizumab administration was not available. PD-L1 expression was measured using a prototype immunohistochemistry assay with an anti-PD-L1 22C3 antibody.

3. Discussion

HPD is known as rapid tumor progression under ICIs treatment and is a deleterious side effect of these drugs [1–5]. HPD prevalence is reported to be 8–14% in NSCLC [3,5]. Reported HPD prediction factors include advanced age [2], MDM2 and EGFR gene mutations [4], and more than two metastatic sites [5]; however, sufficient evidence is not available. The current case was 65 years old and had more than two metastatic sites, but EGFR gene mutations was negative.

When pulmonary lesions worsen during ICIs treatment in NSCLC, pseudoprogression or ILD must be suspected [4]. Pseudoprogression is observed in 4.7% [5], and ILD was seen in 5.8% of NSCLC cases [6]. In this case, ILD by pembrolizumab was suspected at first, and steroids were administered. The ground glass shadows improved in response to the steroid, but the primary lung tumor enlarged. It was difficult to differentiate HPD, pseudoprogression, and ILD from the clinical course and chest HRCT images. At autopsy, inflammatory cell infiltration was poor, and increased cancer and lymphangitic carcinomatosis findings were confirmed. By adding pathological findings, we were confident that the increase in the primary tumor size and surrounding ground glass shadows were caused by the tumor, and concluded that HPD but not pseudoprogression occurred in this case. We think the HPD was related to pembrolizumab therapy. Previous study suggests that HPD is more common with PD-1/PD-L1 inhibitors compared with chemotherapy in pretreated patients with NSCLC [5]. The patient also received chemotherapy, but tumor growth occurred after the first-line treatment with pembrolizumab, it was prior to additional chemotherapy. Further, the speed of tumor growth was significantly increased after pembrolizumab administration.

However, little is known about HPD pathology. We compared PD-L1 expression between the pretreatment and posttreatment conditions. Based on the autopsy results, tumor PD-L1 expression in the subcarinal lymph node decreased significantly, from 98% in the pretreatment condition into 1% in the posttreatment condition. Although data on pretreatment tumor PD-L1 expression in the primary lung cancer

specimen was not available, it was approximately 1% at autopsy. Pathology of the lungs revealed widespread progression of the cancer cells into the alveolar spaces and lymphangitic carcinomatosis. We considered several hypotheses. First: There is a possibility that abrupt proliferation of PD-L1-negative cancer cells after PD-L1-positive cancer cells were affected by PD-L1 inhibitor. Ferrara et al. investigated that the addition of chemotherapy to PD-1/PD-L1 inhibitors may interfere with PD-1/PD-L1 inhibitor resistance and HPD [5]. However, we also consider other possibilities. Second: Tumor PD-L1 expression may be altered by cytotoxic anticancer drugs or irradiation [7,8]. Although the mechanism is not clear, it has been reported that EGFR tyrosine-kinase inhibitor therapy increases PD-L1 expression in some NSCLC patients harboring EGFR mutations [8]. In contrast, pembrolizumab administration may have the potential to reduce PD-L1 expression. Third: There is a possibility that tumor PD-L1 expression may differ depending on different cancer tissue parts in relation to the heterogeneity of the tumor [9]. Fourth: Autopsy was performed 8.5 hours after death, which may have led to post-mortem changes in the cancerous tissues. The definitive cause of the changes in tumor PD-L1 expression in this patient requires further investigation.

Shinozaki et al. reported an autopsy case of pulmonary adenocarcinoma, showing rapid progression of peritoneal dissemination with tumor embolism, in the lung following ICI treatment [10]. In this case, DVT, pulmonary artery thromboembolism, and DIC occurred. We do not know whether these events are related to HPD, and we require additional cases with thorough pathological examination.

4. Conclusion

We describe an autopsy case of HPD after pembrolizumab treatment with pathological examination. Pathology reveals that PD-L1 expression may change after pembrolizumab treatment. Also, the tumor growth or ground glass shadows on chest imaging, appearing after pembrolizumab administration, suggest a possibility of HPD.

Disclosure

All authors have no potential COI to disclose.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors would like to thank Dr. Takeshi Johkoh (Kinki Central Hospital of Mutual Aid Association of Public-School Teachers, Itami, Japan) for his advice on the radiologic images.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2019.100885>.

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