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Case report

Immune-related adverse events caused by treatment with pembrolizumab in a patient with lung cancer who infected influenza virus

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ABSTRACT

A 67-year-old man with stage IV B lung adenocarcinoma was treated with pembrolizumab. The patient was admitted to the hospital because of influenza on the day of the second cycle of pembrolizumab treatment. He was diagnosed with pneumonia and was treated with antiviral drugs and steroids. However, the patient eventually died. In this case, treatment with immune checkpoint inhibitors might have affected the immune response caused by influenza virus infection, that might have caused lung injury, which is an immune-related adverse event (irAE). Hence, it is important that, caution should be taken to prevent transmission of viral infection, and Therefore, it is important to prevent viral infections, but caution should also be paid to the possibility that infections may cause irAEs in patients with lung cancer.

1. Introduction

In Japan, the use of immune checkpoint inhibitor (ICI) for the treatment of lung cancer was approved in December 2015. Then, ICI has become a key chemotherapeutic drug for lung cancer. However, it may cause immune-related adverse events (irAEs), which are often challenging to treat. Herein, we present a patient with interstitial lung disease treated with pembrolizumab who acquired influenza.

2. Case presentation

A 67-year-old man with diabetes mellitus who presented with atelectasis in the right lung was admitted to our hospital. The patient had a smoking history of 10 pack-years. Based on previous examination results, the patient was diagnosed with cT2aN3M1c stage IV B lung adenocarcinoma of the right upper lung. Right malignant pleural effusion was present, for which drainage was performed. The tumor proportion score was 100%, and there were no driver mutations. Therefore, pembrolizumab was used as the first-line treatment.

On the day of the second cycle of pembrolizumab, the patient was admitted to the hospital due to fever and hypoxemia.

Before treatment with pembrolizumab, the patient's carcinoembryonic antigen (CEA) level was 1574.3 ng/mL. However, it decreased to 860.5 ng/mL upon admission. The therapeutic effect of chemotherapy showed stable disease by computed tomography (CT) (Fig. 1). The Krebs von den Lungen-6 (KL-6) level was slightly elevated at 647 U/mL, and the pulmonary surfactant protein D level was normal (17.2 ng/mL). Chest radiography revealed a mass in the right upper lung and consolidation in the left lung (Fig. 2a). CT scan showed ground-glass opacity in the left lung (Fig. 2b). The influenza virus antigen test result was positive for influenza virus type A antigen.

The patient was then treated with peramivir as his pneumonia was caused by the influenza virus. To manage respiratory failure, oxygen administration was initiated at a flow rate of 3 L/min using a face mask and methylprednisolone was administered at a dose of 40 mg/day. On the 2nd day of hospitalization, his body temperature decreased. However, the oxygen flow rate was maintained at 3 L/min as the patient's respiratory status did not improve. Methylprednisolone was discontinued on the 3rd day of hospitalization, and treatment was switched to prednisolone at a dose of 30 mg/day on the 4th day of hospitalization. However, on the 8th day of hospitalization, the oxygen flow rate was increased to 4 L/min. Then, chest CT scan was performed on the 9th day of hospitalization, and results showed enlargement of ground-glass

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Abbreviations

irAE	an immune-related adverse event
ICI	immune checkpoint inhibitor
CAE	carcinoembryonic antigen
KL-6	krebs von den Lungen-6
CT	computed tomography
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2

pneumonia was challenging to confirm. Moreover, there are only few reports on influenza in a patient receiving ICI treatment. Hence, this case is considered valuable.

Recent studies have shown that ICI is effective for the treatment of various cancers, including lung tumors. In the management of lung cancer, ICI is used as not only a single agent but also in combination with other chemotherapeutic drugs. In addition, this drug plays a central role in the treatment of lung cancer, and it can be used as first-line treatment, second-line treatment, and maintenance therapy after chemoradiation therapy.

Although ICI is effective, some studies have shown the occurrence of irAE associated with this drug. In patients with non-small cell lung cancer treated with pembrolizumab, the incidence rates of interstitial

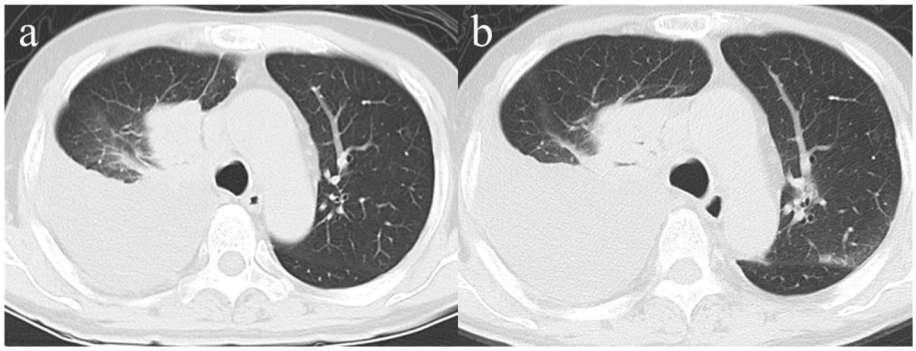

Fig. 1. Computed tomography. a: before treatment of immune checkpoint inhibitor, b: on admission.

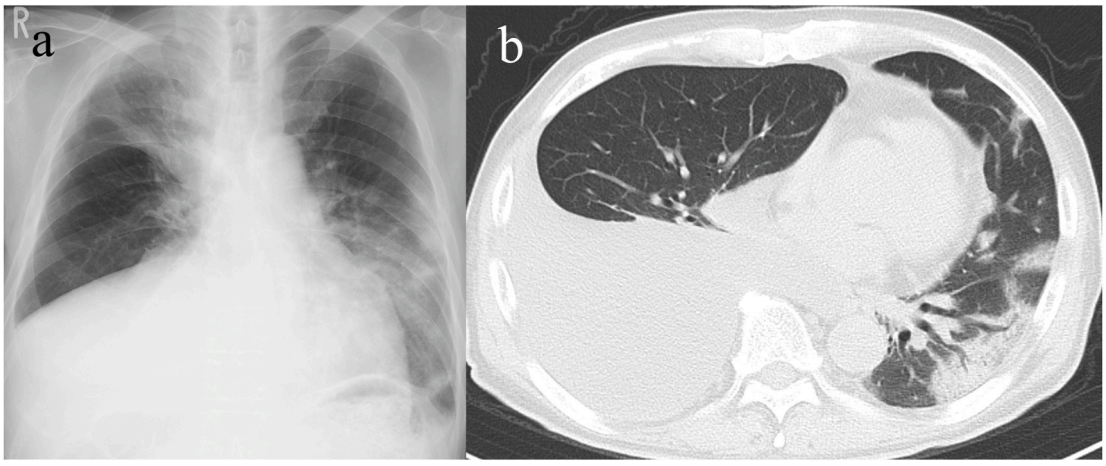

Fig. 2. Chest imaging on admission. a: Chest radiography. b: computed tomography.

opacity in the left lung (Fig. 3). Therefore, treatment with methylprednisolone at a dose of 1000 mg was started. On the 10th day, the oxygen flow rate was further increased to 5 L/min. Pleural effusion was drained considering that the respiratory failure resulted from the pleural effusion. However, despite this, the patient's respiratory condition did not improve. On the 11th day of hospitalization, despite treatment with methylprednisolone, respiratory failure progressed rapidly and morphine administration was initiated for the management of dyspnea. The patient eventually died on the 12th day of hospitalization.

3. Discussion

In this case report, the patient died due to influenza while on treatment with pembrolizumab. Whether the cause of death was lung injury, which is an irAE associated with influenza, or severe influenza virus lung disease are 4.1%–7.0% in those with all grade and 2.1%–3.0% in those with grade 3 or higher. The median onset time is 65.5 (range: 5–816) days [1–3]. Additionally, there are various types of irAE; for example, Chopra A et al. reported a drug-induced sarcoidosis-like reaction [4]. Therefore, in the treatment of ICI, one must be cautious regarding the occurrence of irAE during the course of treatment.

Pembrolizumab is an antibody against programmed cell death-1 (PD-1), which is associated with immune responses. PD-1 is expressed on activated T and B cells. Moreover, it has two ligands: programmed death-ligand 1 (PD-L1), which is expressed broadly on hematopoietic and parenchymal cells, including pancreatic islet cells, and programmed death-ligand 2 (PD-L2), which is restricted to macrophages and dendritic cells. Both ligands play an important role in maintaining immune tolerance [5].

Some studies have reported an association between viral infection

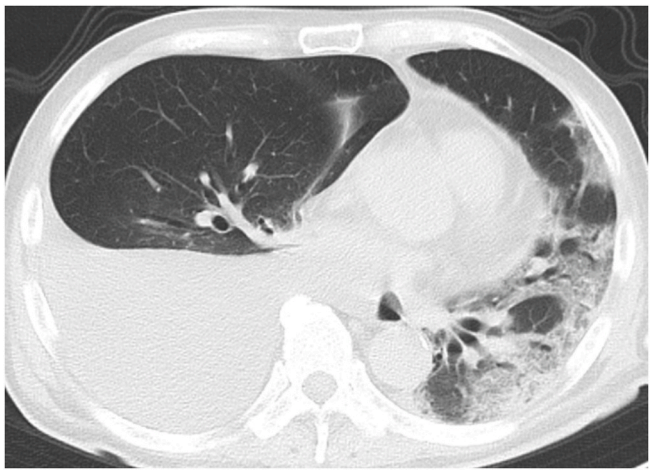

Fig. 3. Computed tomography on the 9th day of hospitalization.

and PD-1. In chronic virus infections, PD-1 expression increased on the surface of regulatory T cells [6], and it contributed to immune tolerance in $CD8^+$ T cells [7]. Even in acute virus infection, including influenza, PD-1 expression on $CD8^+$ T cells is elevated [8]. Therefore, PD-1-mediated immune tolerance might occur in both chronic and acute infections. John A et al. revealed that the use of anti-PD-1 antibody enhances T cell function and improves viral clearance in severe influenza [9]. This result indicated that anti-PD-1 antibody might be effective for the treatment of virus infection. In addition, activated $CD8^+$ T cells produced cytokines and eliminated virus-infected cells [10]. Therefore, if there is excessive immune response, lung injury may occur. However, overproduction of cytokines can cause systemic disorders such as lung injury [11]. Therefore, it is considered that viral infection during ICI treatment may increase cytokine production compared to infection without ICI treatment, which may result in lung injury.

On one hand, in cancer patients with or without ICI treatment, serious complications from influenza can occur. Cooksley et al. reported that about 9% of cancer patients who were hospitalized due to influenza die. Therefore, influenza vaccination is recommended for this group of patients [12]. However, the efficacy and safety of influenza vaccination during ICI treatment has not yet been validated. In the study of Heinz et al., the vaccination groups had a higher number of adverse events than the control group [13]. Nevertheless, Dirk et al. reported that in patients with cancer treated with nivolumab, there was no significant difference in the incidence of irAEs or severe adverse events between the influenza vaccination group and non-vaccination group (irAEs: 26% vs 22%, severe adverse events: 7% vs 4%) [14]. Similarly, Curtis R et al. showed that the incidence of adverse events did not increase in 370 vaccinated patients with cancer treated with ICI [15].

In our case, the patient did not receive influenza vaccination. Whether the patient died of pneumonia associated with the influenza virus or of lung injury, which is a severe irAE, was challenging to confirm. CT features of influenza pneumonia and lung injury associated with irAE have been reported. The predominant CT findings in influenza pneumonia were bilateral, peripheral, ground-glass opacities and/or bilateral areas of consolidation [16]. On the other hand, the CT findings in lung injury associated with irAE were ground-glass opacities, consolidation, bronchiectasis, interlobular septal thickening and intralobular lines. These findings were present in both diffuse lung involvement or localized lung involvement [17]. However, as the CT findings of both the conditions are similar, it is not possible to distinguish them clearly. In our case, the CT findings were ground-glass opacities confined to the left lung, and it was difficult to determine which condition was more likely. Therefore, we considered the clinical course of the patient for determining the most likely condition. In cases of death due to influenza pneumonia, Takayanagi et al. reported that five out of eight cases died within four days after admission [18]. In lung injury as associated with irAE, Jarushka N et al. reported five cases of death [19]. Although the number of days since the onset of irAE was not stated, one patient died due to recurrent pneumonitis during corticosteroid administration was tapered and three patients died as a result of infection due to immunosuppression performed to treat pneumonitis. Two of the three patients had been treated with long-term corticosteroids and immunosuppressants for lung injury. In addition, Sawai et al. reported a case [20] that died 21 days after the onset of lung injury, and Oda et al. reported a case [21] that died 23 days after the onset of lung injury. Therefore, lung injury associated with irAE does not always result in death within a few days after onset. In this case, patient died on the 12th day after the onset of lung injury. The degree of respiratory failure in the patient remained unchanged for 7 days after admission, and despite treatment with anti-influenza drugs, it rapidly deteriorated on the 8th day. Therefore, we considered that the lung injury was associated with irAE. In viral infection, PD-1 expression on $CD8^+$ T cells was enhanced to suppress excessive immune response. Therefore, it is considered that, even in our case, there was a mechanism that worked to prevent an excessive immune response after influenza infection, but an excessive immune response occurred because the immune tolerance mediated by PD-1 was inhibited by ICI treatment, which ultimately resulted in lung injury. Reports on the development of irAEs caused by viral infection during ICI treatment are limited, and the incidence of irAEs has not been validated. As in our case, patients may die due to infection. Hence, more studies about the association between ICI and viral infection or the efficacy of influenza vaccination should be conducted in the future.

4. Conclusion

Viral infection during ICI treatment may be a risk factor of irAEs. Therefore, caution should be taken to prevent transmission of viral infection, and one must be knowledgeable on not only the symptoms of influenza but also the development of irAEs in cancer patients.

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