Case report

Severe tracheal stenosis after first administration of pembrolizumab rescued by Dumon Y-stent in a lung cancer patient

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\begin{abstract}
A 70-year-old woman diagnosed with advanced, non-resectable programmed cell death ligand 1-positive-non-small-cell lung carcinoma was treated with pembrolizumab as first-line therapy. Soon after therapy initiation, she presented with severe dyspnea, and chest computed tomography revealed a soft tissue mass in the lower trachea of the right main bronchus. During bronchoscopy, she became severely hypoxic, and we performed endoscopic tumor ablation and Dumon Y-stent placement. We considered this severe deterioration caused by pseudoprogression, and suggest that it is necessary to perform bronchoscopy and to prepare for the bronchial intervention when treating patients with immune checkpoint inhibitors.
\end{abstract}

1. Introduction

Lung cancer is the leading global cause of cancer-related mortality [1]. In Japan, lung cancer caused nearly 60,000 cancer patient deaths in 2014, representing a significant clinical burden, and the mortality rate continues to increase [2]. Current first-line treatment decisions for advanced or metastatic non-small-cell lung cancer (NSCLC) are based on the presence of driver gene mutations, such as sensitizing mutations of epidermal growth factor receptor (EGFR), translocation of anaplastic lymphoma kinase (ALK), chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase, and programmed cell death ligand 1 (PD-L1) expression on tumor cells [3]. Pembrolizumab, a humanized monoclonal antibody against PD-L1, has replaced cytotoxic chemotherapy as the first-line treatment among patients in whom the percentage of tumor cells with membranous PD-L1 staining (tumor proportion score) is $\geq 50\%$ [4]. Recently, unique cases with a paradoxical deterioration of the disease after immunotherapy have been reported [5,6]. These have been described as cases of pseudoprogression (PP). In one study, PP was observed in 2% of patients treated with immune checkpoint inhibitors (ICIs) [6]. Here we first report a case of PD-L1-positive lung cancer presenting as severe tracheal stenosis, caused by PP after first administration of pembrolizumab, rescued by a Dumon Y-stent.

2. Case report

A 70-year-old woman visited a regional hospital with a productive cough and lymphadenopathy of her left neck. She had a history of smoking 20 cigarettes daily for the past 40 years. Her medical history was unremarkable. Chest radiography revealed a tumor shadow in the right lung apex and multiple bilateral lung nodules. Lung cancer was suspected, and she was referred to Miyazaki Prefectural Miyazaki Hospital for further examination, where she was diagnosed with NSCLC by core-needle biopsy from her left supraclavicular lymph node. The tumor cells were immunohistochemically positive for CK7 and AE1/AE3 but negative for CK20, thyroid transcription factor 1, and p40. Neuroendocrine markers synaptophysin, chromogranin A, and CD56 were not expressed, and EGFR gene mutations and ALK gene translocations were undetected. The tumor tested 75% positive for PD-L1 expression using the anti-PD-L1 antibody clone 22C3. The chest radiograph showed a nodule in the middle of the right lung, mediastinal lymphadenopathy, and tracheobronchial stenosis. Computed tomography (CT) revealed a solitary 2.0-cm pulmonary mass in the right lower lobe and lymphadenopathy in the mediastinum (Fig. 1). The interval between CT at the...
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former hospital and CT at our hospital was about 2 weeks, but no progression was observed. The TNM stage was cT1bN3M1c (brain, lymph nodes) stage IV [7], and the patient was treated with pembrolizumab as first-line therapy.

Soon after pembrolizumab therapy initiation (day 12), the patient visited our hospital for emergency care, complaining of a productive cough and dyspnea. Her vital signs were as follows: temperature, 36.8°C; blood pressure, 132/83 mmHg; pulse, 107/min; and respiratory rate, 20/min with a reduced O2 saturation of 86% on room air. Her chest exam revealed decreased breath sounds in the right lower lung and diffuse inspiratory and expiratory wheezes. Hemogram results revealed a normal leucocyte count of 11,150/μL, and the renal and liver parameters were normal. The LDH and C-reactive protein levels were increased at 387 IU/L and 1.23 mg/dL, respectively. The chest CT revealed a soft tissue mass in the lower trachea to the right main bronchus. (Fig. 2). There were several enlarged mediastinal lymph nodes, but no progression was observed. Bronchoscopy confirmed a soft tissue mass obstructing the lower trachea to such an extent that it impossible to explore the right main bronchus (Fig. 3). We presumed that the patient’s tracheal stenosis was due to tumor invasion of the trachea lumen from the mediastinal lymph node. Because the patient became severely hypoxic by tracheal stenosis during the bronchoscopy, we decided on prompt bronchial intervention.

The patient underwent endoscopic tumor ablation and stent placement using a Dumon rigid bronchoscope (Efer Medical, La Ciotat Cedex, France) under general anesthesia. At the start of the intervention, disappearance of the endotracheal-endobronchial soft tissue was observed. Endoscopically, rough soft tissue rose from the right tracheal wall, and mucosal erosion with edema was found in the tracheal and right main bronchus. We performed argon plasma coagulation and microwave coagulation therapy for mass reduction, and at the end of these procedures, the tracheal and the right main bronchus lumen were re-established using a Dumon Y-stent. We did not perform a tumor biopsy in consideration of the patient’s safety. The Dumon Y-stent placement resulted in dilation of the stenotic trachea and right main bronchus, and the patient’s feeling of dyspnea disappeared. Twenty-four days after stent placement, she received a second course of pembrolizumab. Chest X-ray and CT results after stent placement and two cycles of pembrolizumab were improved (Fig. 4), and she was discharged. After 21 courses of pembrolizumab treatment, she achieved a partial response and has maintained a good health condition for 18 months.

3. Discussion

To our knowledge, this is the first report of serious airway stenosis by PP after first administration of first-line pembrolizumab and the first
that warns about the occurrence of serious deterioration by PP. ICIs, such as anti-programmed cell death 1 (PD-1) antibodies, have transformed lung cancer treatment. Pembrolizumab, a monoclonal antibody targeting PD-1, is effective for some advanced cancers including NSCLC. In a phase three clinical trial, pembrolizumab significantly prolonged overall survival compared with first-line platinum-based chemotherapy in NSCLC patients whose tumors expressed a PD-L1 tumor proportion score ≥50%, and the use of pembrolizumab is rapidly increasing as first-line chemotherapy (4). However, in some cases, its use can result in PP, a phenomenon where the tumor temporarily increases and then shrinks. In some cases, PP is accompanied by severe clinical deterioration, even to a life-threatening degree [8], making it difficult to judge whether treatment should be continued. In our patient, no progression was observed between initial CT at the former hospital and CT at our hospital taken at intervals of about 2 weeks. But acute exacerbation was occurred about 1 week after first pembrolizumab administration. Considering these clinical course of our patient, we have concluded that this severe deterioration was PP. The precise mechanism of PP remains unclear, but it may reflect immune cell infiltration [9,10]. We did not perform a tumor biopsy at that event in consideration of the patient’s safety, so there was no histologic evidence. But we think that performing a biopsy as much as possible leads to the elucidation of the pathological condition.

The state of the tracheal or bronchial invasion is unknown because we did not perform bronchoscopy prior to treatment. Thus, it is necessary to perform bronchoscopy prior to treatment and to prepare for bronchial intervention when treating patients with ICIs in whom there is a large tumor burden around the central airway or where there is a direct invasion of the central airway.

Silicone stents (e.g., Dumon stent) and self-expandable metallic (SEM) stents are widely used [11] for airway stenosis. Silicone stents are strong in expansion power and are removable. We selected a Dumon Y-stent for this patient because the lesion was located in the trachea, carina, and right main bronchus. However, silicone stents require rigid bronchoscopy and general anesthesia for placement. In Japan, institutions that can use rigid bronchoscopes are limited [12]. On the other hand, SEMs can be placed by video-bronchoscopic or radioscopic guidance under local anesthesia, but they are less readily removed. Recently, the AERO™ stent (Alveolus, Inc., NC, USA) was approved in Japan. This hybrid stent was launched in late 2016 [13] and combines the best features of silicone and metal stents with an entirely covered nitinol framework. It is necessary for us to understand the characteristic of these stents before treating patients with severe central airway stenosis.

In conclusion, we experienced a patient with lung cancer presenting with severe tracheal stenosis after first administration of pembrolizumab and rescued her by Dumon Y-stent placement. We consider this severe deterioration caused by PP and suggest that it is necessary to perform bronchoscopy and to prepare for the bronchial intervention when treating patients with ICIs in whom there is a large tumor burden around the central airway or there is a direct invasion of the central airway.

Declaration of interest

Daisuke Himeji received honorarium from Astra Zeneca.

COI statements

All of the authors, except one, report they have no conflict of interest to disclose. One (D.H.) has received honoraria for speaking at an event organized by the Astra Zeneca.

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6. References

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