Nivolumab therapy for lung cancer with tracheo-parenchymal fistula
A case report

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Abstract

Rationale: Tracheobronchial fistulas are rare complications in lung cancer patients. These lesions are associated with a high rate of mortality caused by infection and bleeding, and there is no consensus on a definitive optimal therapy.

Patient concerns and diagnoses: The patient was a 59-year-old man with a right lung mass showing mediastinal invasion and tracheal compression, diagnosed with adenocarcinoma, cT4N0M0, stage IIIA. He was treated with concurrent chemoradiation therapy with carboplatin and paclitaxel, and the lesion markedly shrank. Eleven months later, the lesion showed regrowth, and he underwent repeated chemotherapy for stabilization of the lesion. Thirty-six months after the first regrowth, the tumor showed regrowth again. The patient was then administered docetaxel and bevacizumab as fifth-line therapy. After 11 cycles of docetaxel and bevacizumab therapy, a tracheo-parenchymal fistula appeared.

Interventions and outcomes: Docetaxel and bevacizumab therapy was stopped, and nivolumab therapy was initiated. Subsequently, the fistula and cavity became stable with slight shrinkage. To date, the patient is alive with no complaints and no disease progression and has continued nivolumab for a total of 28 months.

Lessons: Immune-checkpoint inhibitor therapy involving nivolumab therapy might be a useful alternative for the treatment of lung cancer involving a tracheobronchial fistula.

Abbreviations: ALK = anaplastic lymphoma kinase, CEA = carcinoembryonic antigen, CT = computed tomography, EGFR = epidermal growth factor receptor mutation, NSCLC = non-small cell lung cancer, ROS1 = c-ros oncogene 1.

Keywords: immune-checkpoint inhibitor, lung adenocarcinoma, nivolumab, tracheo-parenchymal fistula

1. Introduction

Acquired fistulas of the tracheobronchial airways are a relatively rare complication in lung cancer patients.[1–4] Among them, tracheo-mediastinal-parenchymal fistulas are especially rare, and only a few cases have been reported.[1,2] Tracheobronchial fistulas related to malignant conditions are associated with a high rate of mortality caused by infection and bleeding,[1–4] and there is no consensus on a definitively optimal therapy.[1] Therapies such as intratracheal stent insertion[1,4] and supportive care[2,3] are selected based on the characteristics of each case; however, these therapies are only palliative, and inadequate for long-term survival. In addition, treatment using adipose-derived stem cells has been reported,[3] however, this is an experimental therapy.

Nivolumab is an immune-checkpoint inhibitor and has shown efficacy for previously treated non-small cell lung cancer (NSCLC).[6,7] Therefore, nivolumab therapy has become one of the standard therapies for these patients. Herein, we report a case of tracheo-parenchymal fistula in lung adenocarcinoma stabilized by nivolumab therapy.

2. Case report

A 59-year-old man with a 59-pack-year smoking history was referred to our hospital with a right lung mass on chest X-ray and computed tomography (CT) scan. The mass showed mediastinal invasion and tracheal compression (Fig. 1A). No endotracheal invasion was detected with a bronchoscopic examination. Laboratory examinations revealed elevated levels of carcinoembryonic antigen (CEA; 129.8 ng/mL). The patient underwent an endobronchial ultrasonography-guided transbronchial needle aspiration, and the tumor was diagnosed as an epidermal growth factor receptor mutation (EGFR)-negative adenocarcinoma via cytological and genetic examination. However, since no biopsy specimen could be obtained, anaplastic lymphoma kinase (ALK) gene rearrangement, c-ros oncogene 1 (ROS1)
rearrangement, and programmed death-ligand 1 (PDL1) expression could not be examined. After further examination, he was diagnosed with adenocarcinoma, cT4N0M0, stage IIIA. He was treated by concurrent chemoradiotherapy with carboplatin and paclitaxel. Subsequently, a chest CT revealed marked reduction of the tumor diameter (Fig. 1B).

Eleven months after the start of chemoradiotherapy, the tumor showed regrowth. Therefore, post-regrowth first-line chemotherapy with carboplatin and pemetrexed was performed, and the lesion shrank. However, the tumor later showed local regrowth, and the patient was administered cytotoxic drugs, including gemcitabine, vinorelbine, and docetaxel, after which the lesion stabilized. During this period, no cavity formation and endobronchial invasion were observed in the lesion.

Thirty-six months after the first regrowth, the tumor showed regrowth again. Therefore, the patient was administered docetaxel and bevacizumab as the fifth-line therapy. After 7 cycles of docetaxel and bevacizumab therapy, the lesion appeared stabilized on CT; however, after 11 cycles, a tracheo-parenchymal fistula was detected (Fig. 2A, B). The CT scan showed a fistula connecting the trachea to the upper lobe of the right lung at a site where the lung cancer lesion had a thin-walled cavity formation. Docetaxel and bevacizumab therapy was interrupted due to suspicion that the chemotherapy might have caused the fistula and cavity formation, and that continuation of the chemotherapy might increase the risk of infection of the fistula and cavity. Two months later, the lesion had worsened slightly, and the serum level of CEA increased from 6.5 ng/mL to 8.8 ng/mL, therefore, we determined that the fistula and cavity formation had been related to the regrowth of the tumor lesion. Anticancer treatment was required for stabilization of the tracheo-parenchymal fistula. At the time, the Eastern Cooperative Oncology Group performance status of the patient was 1. The patient was administered nivolumab at 3 mg/kg every 2 weeks.

Figure 1. CT before (A) and after (B) chemoradiotherapy. The CT scans showed marked shrinkage of the lung cancer lesion. CT = computed tomography.

Figure 2. Horizontal (A) and three-dimensional (B) views of a CT scan obtained after 11 cycles of docetaxel and bevacizumab therapy. The CT scan showed a fistula in the tracheo-upper lobe of the right lung, and the lung cancer lesion with thin-wall cavity formation. CT = computed tomography.
weeks (recommended dose and schedule for NSCLC therapy[6,7]), and the fistula and cavity became stable without any remarkable adverse event. Twenty-six months later, the lesion showed slight shrinkage on CT examination (Fig. 3A, B), and the serum level of CEA also improved (1.5 ng/mL). To date, the patient is alive with no complaints and no disease progression and has continued nivolumab treatment for a total of 28 months.

Written informed consent was given by the patient.

3. Discussion

In this case report, we present 2 important clinical observations. First, tracheobronchial fistulas in lung cancer can occur suddenly, even if the lesion has been stabilized for a long time by continuation of chemotherapy. Risk factors associated with bronchial fistulas include radiotherapy, histopathological type of tumor (e.g., squamous cell carcinoma), superimposed infections, and treatment with anti-angiogenic factors (e.g., bevacizumab).[1–4] To the best of our knowledge, there has been no report of a relationship between the period/dosage of chemotherapy and formation of tracheobronchial fistula. In the present case, chemoradiotherapy and bevacizumab administration might have been related to the formation of the tracheo-parenchymal fistula.

Second, immune-checkpoint inhibitor therapy might be a useful alternative for the treatment of lung cancer involving a tracheobronchial fistula. It is assumed that tracheobronchial fistula formation is related to several factors, such as destruction of pre-existing tissue structures by tumor invasion and/or bacterial infection, and weakening of airway wall integrity.[1] Therefore, for the stabilization of a tracheobronchial fistula, the treatment requires several conditions, as follows: a sufficient anticancer effect; low risk of bacterial infection; and low risk of promotion of weakening of airway wall integrity. Immune-checkpoint inhibition has been shown to be effective for NSCLC, and less toxic, as well as less likely to lead to infections, than cytotoxic drugs,[6–9] and there is no report of an effect of weakening airway wall integrity. Nivolumab therapy was selected for the present case, and fortunately it was effective.

Immune-checkpoint inhibitor therapies, including nivolumab therapy, have several weaknesses, such as insufficient response rate (approximately 20%)[6,7] and probability of causing pseudoprogression[10] or hyperprogressive disease.[11] Effect predictors of immune-checkpoint inhibitor therapies, such as smoking history,[6,7] mutation burden,[12] and programmed cell death-1 ligand 1 expression,[8] should be examined to determine the therapeutic strategy. In addition, the progress of the lesion should be monitored frequently.

For the treatment of lung cancer involving a tracheobronchial fistula, molecular targeted therapy may also be an alternative if the lung cancer has a driver mutation, such as mutations in EGFR,[13] ALK,[14] or ROS1.[15,16] Molecular targeted therapies have shown strong efficacy for NSCLC, and less relation to infection and weakening of airway wall integrity. In the future, progress in genetic examinations and molecular targeted therapy for lung cancer may bring more benefits for the treatment of lung cancer involving a tracheobronchial fistula.

In conclusion, we report a case of tracheo-parenchymal fistula in a lung cancer patient stabilized by nivolumab therapy. Immune-checkpoint inhibitor therapy might be a useful alternative for the treatment of lung cancer involving a tracheobronchial fistula.

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Figure 3. CT after 26 months of nivolumab therapy (A, B). The CT scan showed slight shrinkage of the tracheo-parenchymal fistula lesion. CT = computed tomography.
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