OMCR

Oxford Medical Case Reports, 2020;12,452–455

doi: 10.1093/omcr/omaa116
Case Report

CASE REPORT

Bronchoesophageal fistula formation after three courses of nivolumab for carcinoma of unknown primary with a subgroup of lung squamous cell carcinoma

Akihiro Nishiyama[1,*], Hiroyuki Sakaguchi[1], Naohiro Yanagimura[1], Chiaki Suzuki[1], Sakiko Otani[1], Azusa Tanimoto[1], Kaname Yamashita[1], Shinji Takeuchi[1], Koushiro Ohtsubo[1], Hiroko Ikeda[2] and Seiji Yano[1]

[1]Division of Medical Oncology, Cancer Research Institute, Kanazawa University, Kanazawa, Ishikawa 920-0934, Japan, [2]Department of Diagnostic Pathology, Kanazawa University Hospital, Kanazawa 920-8641, Ishikawa, Japan

*Correspondence address. Division of Medical Oncology, Cancer Research Institute, Kanazawa University, 13-1, Takaramachi, Kanazawa, Ishikawa 920-0934, Japan. Tel: +81-76-265-2794; Fax: +81-76-244-2454; E-mail: an0510@staff.kanazawa-u.ac.jp

Abstract

Immune checkpoint inhibitors (ICIs) are widely used in both monotherapy and combination chemotherapy for various types of cancers. Nivolumab is the most popular among ICIs, and the number of adapted malignant diseases for nivolumab is increasing. Bronchoesophageal fistula formation is a serious complication of the treatment for esophageal or lung cancer. However, the development of bronchoesophageal fistula as a complication of ICIs is obscure. A 59-year-old man who was diagnosed with carcinoma of unknown primary with a subgroup of lung squamous cell carcinoma had bronchoesophageal fistula formation after three cycles of nivolumab as the fourth line treatment. Before the initiation of nivolumab, he had received two esophageal stents and an angiogenesis inhibitor. These are known risk factors for fistula formation. This is a rare case showing that nivolumab monotherapy might induce bronchoesophageal fistulae. Therefore, clinicians should be aware of the factors related to fistula formation when using ICIs.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) target immune checkpoints that suppress the activity of immune cells. There are several types of immune checkpoints, including the programmed cell death 1 (PD-1) protein. ICIs are widely used in both monotherapy and combination chemotherapy for many types of cancer [1, 2]. Nivolumab, which targets PD-1, is one of the most popular ICIs, and the number of adapted malignant diseases for nivolumab is increasing. It has been most recently used in patients with advanced esophageal cancers [3]. Carcinoma of unknown primary site (CUP) is a malignant tumor that is histologically diagnosed as a metastatic lesion, but its primary lesion is unknown despite a full-body examination [4]. In the Special Clinical Science Symposium of ASCO 2020, a phase II trial performed by Kinki University showed that nivolumab was effective in the management of CUP. Clinicians, particularly

Received: August 30, 2020; **Revised:** September 24, 2020; **Accepted:** October 22, 2020

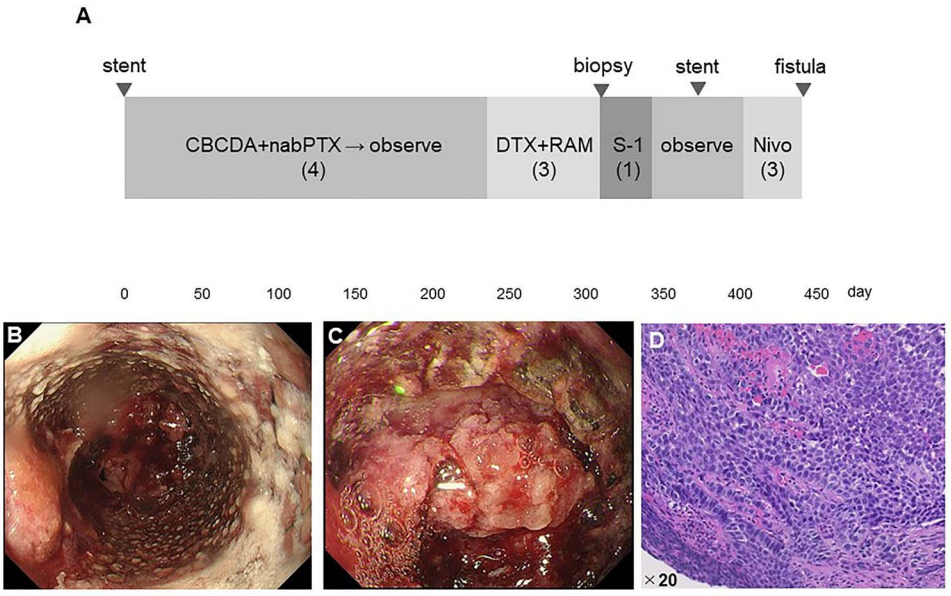

Figure 1: The patient's treatment courses with all events including endoscopic examination of the patient's esophagus. (**A**) (X) refers to the number of conducted courses. CBDCA: carboplatin, nabPTX: nab-paclitaxel, DTX: docetaxel, RAM: ramucirumab, S-1: tegafur/gimeracil/oteracil, Nivo: nivolumab. (**B**) Self-expanding uncovered metal stent and tumor growth within the stent can be identified. (**C**) A close-up picture of the tumor in which biopsy was performed. (**D**) Histological examination of the tumor showed squamous cell carcinoma.

medical oncologists, should have better knowledge regarding the use of ICIs. Bronchoesophageal fistula formation is a severe complication of esophageal or lung cancer, especially following radiation therapy. Although ICIs are associated with a variety of adverse events, the relationship between bronchoesophageal fistula formation and ICIs is unknown.

CASE REPORT

A 59-year-old man who experienced difficulty in swallowing for 4 months underwent upper endoscopy. On examination, no change was observed in the mucosal surface of the esophagus, but we found stricture associated with compression from the outside. Subsequently, he underwent positron emission tomography–computed tomography (CT), and multiple lymph nodes, including the supraclavicular fossa, mediastinal, intraperitoneal and right inguinal nodes, showed ^{18}F-fluorodeoxyglucose accumulation. Because the mediastinal lymph node metastasis was pressing on his esophagus, he underwent esophageal self-expanding uncovered metal stent insertion, and his symptoms improved. A mediastinal lymph node (#7) biopsy conducted by endobronchial ultrasound-guided transbronchial needle aspiration revealed squamous cell carcinoma. However, a whole-body examination could not detect the primary lesion, and he was diagnosed with postoperative recurrence of CUP. Since lung cancer has more treatment options than other cancers, we considered his CUP as a subtype of lung cancer. Figure 1A details his treatment course with some events. Chemotherapy with nab-paclitaxel (100 mg/m^2; Days 1, 8 and 15 in a 4-week cycle) and carboplatin (target area under the curve, 6; Day 1 in a 3-week cycle) was initiated as first-line treatment. Ramucirumab (10 mg/kg, Day 1 in a 3-week cycle) and docetaxel (60 mg/m^2, Day 1 in a 3-week cycle) were administered as second-line treatment. The patient underwent biopsy of the tumor within the esophageal stent, and the tumor was histologically

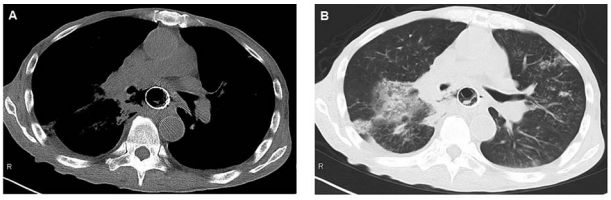

Figure 2: Findings on chest CT. (**A**) Axial CT with mediastinal window pointed out a fistula (arrow) in the truncus intermedius. (**B**) The area around the fistula showed infiltration in the right lower lobe.

determined as squamous cell carcinoma (Fig. 1B–D). Thereafter, the patient was initiated on third-line treatment with S-1 (100 mg/day, Days 1–28 in a 6-week cycle). After one cycle of S-1, the tumor at the lower edge of the esophageal stent grew and the patient often vomited because of obstruction. He underwent esophageal self-expanding covered metal stent insertion at the site of obstruction and could resume eating. Three weeks after stenting, he received nivolumab as fourth-line treatment. After three cycles of nivolumab, he had a high fever and productive cough with purulent sputum. A chest CT showed consolidation along the right bronchus that demonstrated pneumonia and a fistula at the truncus intermedius (Fig. 2). He then underwent bronchoscopy, where we found three bronchoesophageal fistulae (Fig. 3). Furthermore, we placed a third esophageal covered stent to seal the tracheoesophageal communication after the pneumonia improved. However, his left vocal cord got paralyzed due to the enlargement of the left cervical lymph node metastasis, which was found on bronchoscopy examination. Although he underwent dysphagia rehabilitation, he developed aspiration pneumonia. He stopped food intake by his mouth, and underwent gastrostomy. Subsequently, his general condition worsened, and he died from suffocation because of clogging with sputum.

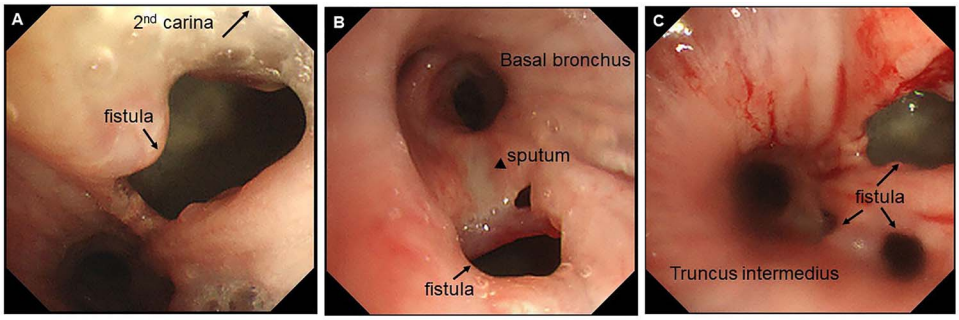

Figure 3: Bronchoscopic examination of the patient's right bronchial tube. (**A**) Under the inset of the right upper lobe, a fistula could be detected. (**B**) In the truncus intermedius, a fistula covered with sputum (arrowhead) could be detected. (**C**) All three fistulae were detected along the caudal end of the truncus intermedius and the area around the fistulae became hemorrhagic.

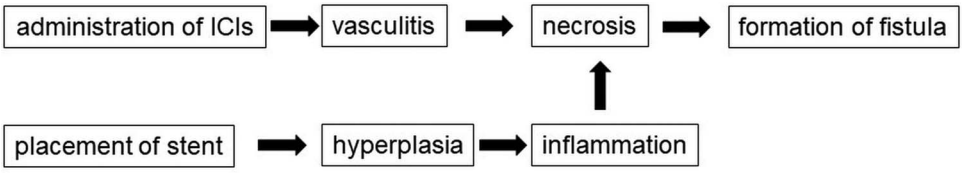

Figure 4: The possible mechanism of fistula formation in our case.

DISCUSSION

We experienced a patient with a CUP favoring lung squamous cell carcinoma who developed bronchoesophageal fistulae after three courses of nivolumab. This therapeutic complication is serious and can be fatal. Recently, it was reported that durvalumab after chemoradiotherapy might cause broncho-mediastinal fistulae in stage III non-small cell lung cancer [5]. However, there are few reports on the relationship between ICIs and fistula formation. Acral vascular necrosis, which indicates small vessel vasculitis and leads to ischemia, was introduced as an immune-related adverse event of ICIs [6]. In this case, given that nivolumab caused vasculitis in the area around the stent, vasculitis might have led to necrosis and fistula formation. Furthermore, in our case, besides nivolumab, two other factors, including the esophageal stent and ramucirumab may have been related to the fistulae. It has been reported that placement of an esophageal stent induces tissue hyperplasia and inflammatory cell infiltration [7]. Since our patient had a second esophageal stent placement before fistula formation, some part of the tissue around the stent may have become necrotic because of the process of inflammation. Furthermore, there are two different reports similar to our case. One report showed that one cycle of pembrolizumab caused tracheoesophageal fistula formation in a patient with squamous cell lung cancer and bronchial stent in the left bronchus [8]. Another study showed that one cycle of pembrolizumab caused esophagobronchial perforations after the placement of an esophageal self-expanding metallic stent in a patient with stage IV lung adenocarcinoma [9]. Based on the above considerations, we might be able to explain the process of fistula formation associated with ICIs (Fig 4). Antiangiogenic agents, such as bevacizumab, are often used in combination chemotherapy for many types of cancers, and there are some reports about fistula formation and delay in wound healing associated with the use of these drugs [10]. In this case, 156 days had passed since the last administration of ramucirumab to the development of bronchoesophageal fistula. Because the half-life of ramucirumab is reported to be ~8 days, ramucirumab is unlikely to be a factor in fistula formation. Thus, administration of ICIs might have triggered fistula formation in this patient. Since there are only a few cases of ICIs and fistulas, the attending physician should check whether the patients have a stent before administration of ICIs.

SUPPLEMENTARY MATERIAL

Supplementary material is available at the *Journal of Surgical Case Reports* online.

ACKNOWLEDGMENTS

We thank the patient and his family for providing informed consent for the processing of his personal data for this publication.

CONFLICT OF INTEREST STATEMENT

S.Y. received honoraria from Chugai Pharmaceutical Co., Ltd and obtained research funding from Eisai Co., Ltd, Noile-Immune Biotech Inc. and obtained subsidies or donations from Bayer Yakuhin, Ltd, Taiho Pharmaceutical Co., Ltd, EliLilly Japan K.K. The other authors have no conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's family for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

GUARANTOR

Akihiro Nishiyama.

REFERENCES

1. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A *et al*. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol* 2019;**37**:537–46. doi: 10.1200/JCO.18.00149.
2. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F *et al*. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;**378**:2078–92. doi: 10.1016/j.ejcts.2010.05.020.
3. Kato K, Cho BC, Takahashi M, Okada M, Lin CY, Chin K *et al*. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicenter, randomized, open-label, phase 3 trial. *Lancet Oncol* 2019;**20**:1506–17. doi: 10.1016/S1470-2045(19)30626-6.
4. NCCN Clinical Practice Guidelines in Oncology. Occult primary (cancer of unknown primary) Version 2. 2016. https://www2.tri-kobe.org/nccn/guideline/archive/occult2013/english/occult.pdf.
5. Sumi T, Ikeda T, Kure K, Yamada Y, Nakata H, Mori Y. Bronchomediastinal fistula during durvalumab therapy after chemoradiotherapy in stage III NSCLC. *J Thorac Oncol* 2019;**14**:1860–1. doi: 10.1016/j.jtho.2019.06.003.
6. Khaddour K, Singh V, Shayuk M. Acral vascular necrosis associated with immune-check point inhibitors: case report with literature review. *BMC Cancer* 2019;**19**:449. doi: 10.1186/s12885-019-5661-x.
7. Kim EY, Shin JH, Jung YY, Shin DH, Song HY. A rat esophageal model to investigate stent-induced tissue hyperplasia. *J Vasc Interv Radiol* 2010;**21**:1287–91. doi: 10.1016/j.jvir.2010.04.023.
8. Wang H, Zhang L, Liu W. Tracheoesophageal fistula caused by successful response to pembrolizumab in a patient with squamous cell lung cancer. *J Thorac Oncol* 2019;**14**:e141–3. doi: 10.1016/j.jtho.2019.02.013.
9. Tomiyama K, Ito N, Hayashi K, Kawamoto Y, Shinoda H, Katakami N. Oesophagobronchial perforations after placement of an oesophageal self-expanding metallic stent. *Resirol Case Rep* 2020;**8**:e00554. doi: 10.1002/rcr2.554.
10. Schreiber J, Waldburg N. Bronchoesophageal fistula and fatal hemoptysis after bevacizumab-containing chemotherapy without radiation in lung cancer. *J Clin Oncol* 2012;**30**:e324. doi: 10.1200/JCO.2012.42.8169.