Oesophagobronchial perforations after placement of an oesophageal self-expanding metallic stent
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Keywords  
Oesophagobronchial perforation, pembrolizumab, pneumonia, self-expanding metallic stent.

Abstract  
An oesophageal fully covered self-expanding metallic stent (SEMS) was placed in a 54-year-old Japanese man to relieve dysphagia owing to a stage cT1bN3M1c lung adenocarcinoma. High expression of programmed cell death-ligand 1 was microscopically confirmed, and pembrolizumab was subsequently administered. Several days later, the patient was hospitalized with septic shock, and severe mediastinitis and pneumonia caused by oesophageal SEMS-induced oesophageal and bronchial perforations were observed. Thoracoscopic surgery was performed to drain the mediastinal abscess, and an additional oesophageal SEMS was placed to close the oesophageal perforation. The patient gradually recovered from the potentially fatal infection, and the SEMS was retrieved after confirming perforation closure. We re-initiated pembrolizumab administration, and the patient responded well. The present report reveals the potential risk and effectiveness of SEMS, especially when administered with immune checkpoint inhibitors.

Introduction  
Placement of an oesophageal self-expanding metallic stent (SEMS) is an established palliative treatment modality for malignant oesophageal strictures, although significant complications, including oesophageal perforation or fistula formation, have been reported [1,2]. However, oesophageal stents have been beneficial in managing oesophageal perforations [2].

Here, we present a case of oesophagobronchial perforation following oesophageal SEMS placement and pembrolizumab administration. To our knowledge, this is the first report on oesophagobronchial SEMS-induced perforation following the administration of immune checkpoint inhibitors (ICIs).

Case Report  
A 54-year-old Japanese man with a month-long history of dysphagia, haemoptysis, and weight loss was admitted to our hospital. He had a history of smoking (30 packs/year). Chest computed tomography (CT) revealed a small nodule in the right lower lobe (Fig. 1A) and remarkable swelling of mediastinal lymph nodes measuring 9 × 5 cm, resulting in the compression of the thoracic oesophagus (Fig. 1B). A poorly differentiated adenocarcinoma was diagnosed based on transbronchial biopsy, and the high programmed cell death-ligand 1 (PD-L1) expression ranged from 90% to 100%. No mutations were detected in driver oncogenes. 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) revealed FDG accumulation in the right lower lung nodule, mediastinal and right supraclavicular lymph nodes, both adrenal glands, and pelvic bone. No brain metastasis was observed on enhanced magnetic resonance imaging; thus, the clinical stage was judged as IVB (cT1bN3M1c). As the patient had severe dysphagia owing to bulky mediastinal lymph nodes, we placed a retrievable oesophageal SEMS, measuring 22 mm in diameter and 10 cm in length, using a gastroscope (Fig. 1C). We decided on the dimension of the SEMS by judging the length of the stricture based on a fluoroscopic radiograph and the diameter of non-stenotic oesophageal portion. According to the latest edition of Guidelines for Diagnosis and Treatment of the Lung Cancer, edited by the
Japan Lung Cancer Society in 2017, we began a solo regimen of pembrolizumab. We administered pembrolizumab (200 mg/body) 18 days after inserting the SEMS, with no appreciable adverse events. Nine days after medication, he was emergently admitted to our hospital with high fever and pharyngeal pain. Laboratory examination results showed a remarkable elevation in serum C-reactive protein levels (25.9 mg/dL; normal range < 0.5 mg/dL) and white blood cells (16,000; normal range < 8300/μL), and he was diagnosed with septic shock. CT revealed free air in the mediastinum and infiltrate in the lungs. The gastroscope revealed a perforation in the oesophagus located immediately above the oral end of the SEMS. The bronchoscope also showed a perforation measuring approximately 1 cm in size in the membranous portion of the left main bronchus near the carina (Fig. 1D). Bronchoscopy also showed a perforation measuring approximately 1 cm in size in the membranous portion of the left main bronchus near the carina (Fig. 1E). The patient was diagnosed with severe mediastinitis with concomitant pneumonia. To drain the mediastinal abscess, we performed thoracoscopic surgery. Although fever was slightly relieved after drainage surgery, pneumonia and empyema caused by an inflow or discharge of saliva through the oesophagobronchial fistula was sustained. We placed a second oesophageal SEMS overlapping the first one to block the oesophageal perforation (Fig. 2A). After the treatment, his respiratory condition recovered, and pleural effusion gradually reduced. As spontaneous closure of perforations could not occur without retrieving the first SEMS, we removed the first and second SEMS and inserted a third SEMS at the same position as the second one using a gastroscope under general anaesthesia 15 days after the drainage. Twenty-seven days after the drainage, the thoracic drainage tube was extubated, and the patient started an oral intake of a fluid diet. CT revealed shrinkage of the lung tumour and the mediastinal mass. We confirmed closure of the bronchial perforation 38 days after the drainage (Fig. 2B), and the oesophageal perforation was healed, as shown by the retrieval of the third SEMS 50 days after the drainage (Fig. 2C). Pembrolizumab administration was re-initiated, and a complete resolution was observed on PET–CT after five courses of the regimen (Fig. 2D).
Discussion

Placement of SEMS is a recommended palliative treatment modality for malignant stenosis in the gastrointestinal or respiratory tract. However, there are many reports on stent-associated fatal complications [1,2], which could be triggered by subsequent medication or radiotherapy. The development of ICIs has dramatically changed the prognosis of patients with advanced non-small cell lung cancer. In some patients, even complete resolution may be achieved with ICIs alone [3]. In our case, the overwhelming response to ICIs induced excessive expansion of the oesophageal SEMS, causing oesophagobronchial perforations. If such an overwhelming response to ICIs had been predicted in advance, we could have adopted surgical gastrostomy for nutrition instead of oesophageal SEMS. However, in contrast to the risk of fatal complications, successful closure of oesophageal perforations has also been reported with a covered stent [2,4]. We also obtained good results by inserting a second and third oesophageal SEMS. Healing of the fistula might be achieved as the oesophageal stricture was formed only by external compression without invasion to the wall.

One of the reasons we could control the fatal infection was that we chose a solo pembrolizumab regimen and not a regimen of platinum-based chemotherapy plus ICIs, which is recommended for driver oncogene-negative PD-L1 ≥ 50% patients by the latest guideline for non-small cell lung cancer stage IV, as edited by the Japanese Lung Cancer Society [5]. If we had used ICIs with cytotoxic chemotherapy, we would not have been able to overcome the septic shock with neutropenia.

Further investigation of predictors of response to ICIs besides PD-L1 is desirable to reduce adverse events of dispensable treatment options.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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