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RESPIRATORY CASE REPORTS

Tracheoesophageal Fistula Associated with Nivolumab

Nivolumab İlişkili Trakeaözefagial Fistül

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Abstract

Tracheoesophageal fistula (TEF) is a pathological connection between the trachea and the esophagus that can be congenital or can develop in older ages as a result of benign or malignant causes. It develops as a result of mediastinal invasion or after chemoradiotherapy in lung and esophageal cancers, and is associated with high mortality and morbidity. TEF has been reported in the past to be a rare side effect of immune control inhibitor (ICI) drugs used for the treatment of non-small cell lung cancer, and several cases have been reported. A 78-year-old patient who underwent a left pneumonectomy after being diagnosed with NSCLC one year earlier had a history of esophageal stenting and Nivolumab use two months previously to relieve the pressure of a mediastinum mass invading the esophagus that was causing dysphagia in the patient. The patient developed TEF in the first week of hospitalization, which was thought to be a side effect of the ICI drugs. Our case, who was thought to place a stent in the trachea, died after developing massive hemoptysis. We present this case of the development of TEF to literature due to its rarity as a side effect of ICI drugs.

Key words: *Tracheoesophageal fistula, lung cancer, immunotherapy.*

Öz

Trakea ve özafagus arasında patolojik bir bağlantı olması trakea-özafagiyal fistül (TÖF) olarak adlandırılır, doğuştan veya bening ya da maling nedenlere bağlı sonradan oluşabilmektedir. TÖF, akciğer ve özefagus kanserlerinde kemoradyoterapi sonrası veya mediastinal invazyon nedeni ile gelişen, yüksek morbidite ve mortaliteye neden olan bir komplikasyondur. Son yıllarda Non-small cell akciğer kanseri (NSCLC) tedavisinde immun kontrol inhibitör (ICI) ilaçların kullanımının artışına bağlı nadir görülen yan etkiler ortaya çıkmakta ve olgu bazında bildirilmektedir. Yetmiş sekiz yaşında bir yıl önce NSCLC tansı ile sol pnömonektomi olan olgumuzda mediastene invaze kitlenin özafagusa basısına bağlı disfaji nedeni ile iki ay önce özafagusa stent uygulama ve nivolumab kullanım öyküsü vardı. Yatışının ilk haftasında hastada TÖF gelişti. Trakeaya stent yerleştirilmesi düşünülen olgumuz, masif hemoptizi gelişmesi nedeni ile eksitus oldu. Ayırıcı tanı sonrası ICI ilaça bağlı yan etki olarak TÖF geliştiği düşünüldü. Nadir bir yan etki olarak görülmesi nedeni ile olgumuzu literatür bilgileri ile sunmak istedik.

Anahtar Sözcükler: *Trakeaözefagial fistül, akciğer kanseri, immunoterapi.*

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Tracheoesophageal fistula (TEF) refers to a pathological connection between the trachea and the esophagus that can occur congenitally or later in life, and to have benign or malignant causes (1). TEF, which develops due mediastinal invasion or chemoradiotherapy in lung and esophageal cancers, is associated with high mortality and morbidity. In recent years, immunotherapy has been the standard treatment for melanoma, renal cell carcinoma, Hodgkin lymphoma, bladder, head and neck cancers and lung cancer (2,3), and the use of immunocontrol drugs such as nivolumab has become widespread. In addition to the pulmonary toxicities associated with drugs, rare side effects such as TEF can also be seen. The identification of such life-threatening side effects as TEF in the future will be possible through awareness-raising activities.

CASE

A 78-year-old male patient presented to the emergency department with a complaint of increasing dyspnea for two months. The patient had been a 50 pack-year smoker, but had quit one year earlier. The patient's diabetes was under control, but underwent a left pneumonectomy operation one year earlier for the treatment of non-small cell lung cancer, followed by chemoradiotherapy in the postoperative period. Two months before presenting to our facility the patient had been fitted with a stent in the esophagus to ease his dysphagia and he had been treated with nivolumab since. Five days after hospitalization, the patient's complaints of cough, sputum and shortness of breath increased. A thorax CT, revealed air-fluid level on the left. A tracheoesophageal fistula was observed on the esophageal stent at the level of the carina (Figure 1). The patient was operated with FOB, during which it was found that the stent in the middle 1/3 of the esophagus had eroded the tracheal wall and caused a complete opening into the trachea. Stent placement in the trachea was planned with rigid bronchoscopy (Figure 2), however, the patient died due to the sudden onset of hemoptysis.

DISCUSSION

We present here to literature a rare case of a tracheoesophageal fistula (TEF) caused by Nivolumab – an ICI drug used for the treatment of non-small cell lung cancer. TEF associated with malignancies is a complication with high mortality and morbidity, and generally develops as a side effect of lung cancer, cancer invasion into the mediastinum, or as a side effect of chemoradiotherapy during the treatment of cancer of the esophagus (1).

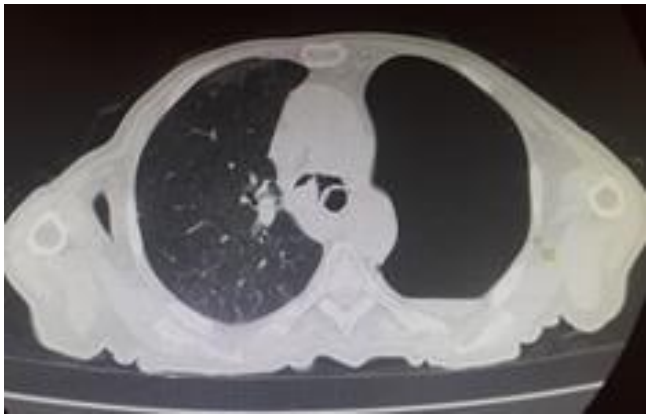

Figure 1: *Thorax CT*

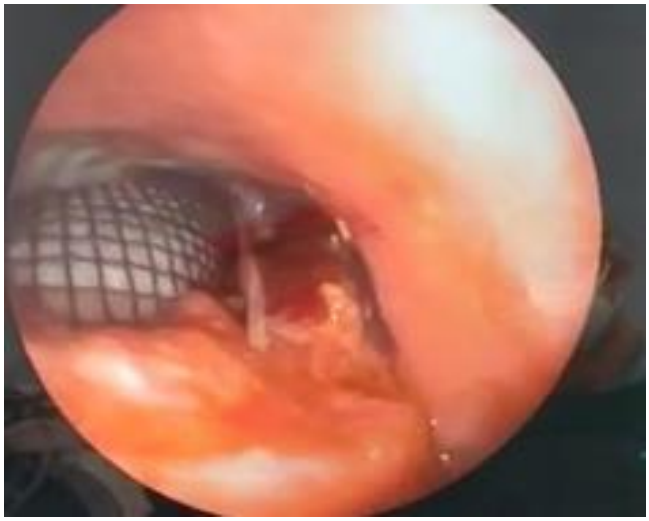

Figure 2: *FOB imaging*

TEF has been reported in 4.5% of esophageal cancers and in 0.3% of lung cancers (4). The male/female ratio is 3/1, and the most common symptoms are cough, aspiration, fever and dysphagia. The fistula localization site is most often in the trachea 53%, left main bronchus 22% and right main bronchus 16%. (5) The European Society of Gastrointestinal Endoscopy recommends the use of metallic coated stents for the treatment of dysphagia due to lung cancer. (1)

In our case, a metal-covered stent had been fitted 2 months earlier due to dysphagia, and nivolumab treatment was started due to tumor progression. Nivolumab is a PD-1 monoclonal inhibitor that was one of the first immune control drugs to be approved for the treatment of small- and non-small cell lung cancer, and it has been widely used in recent years. (3)

Although pulmonary toxicity due to immunocontrol drugs (ICI) is frequently reported in literature, the development of TEF is rare and is reported as a case report (2). The development of a bronchomediastinal fistula was reported in a patient receiving durvalumab following chemora-

diotherapy in stage-3 NSCLC, while the development of TEF due to pseudoprogression and metastatic mediastinal LAM was reported in a patient diagnosed with lung adeno carcinoma who was undergoing nivolumab therapy (6,7).

Pseudoprogression is defined as tumor growth or the development of new foci when the general situation of the patient is stable, with an incidence rate of 3.4–6.9% reported in patients using PD-1 inhibitors for the treatment of non-small cell lung cancer. (8)

Pseudoprogression was not considered in the present case since the patient's general situation did not improve with stent placement and immunotherapy, and there was no growth in the mass invading the mediastinum.

In a retrospective study of stent placement failures in patients with esophageal stents due to benign or malignant reasons, stent over 12 cm in length, stent placement in the 1/3 mid-esophageal area, and dilation before stent placement were reported as risk factors. In the same study, the risk of perforation was 3.3%, the development of fistula was reported to be 2.5–7.9% and the stent failure time was reported to be an average of 75 days after placement (9).

Our case, who had DM, had a 4 cm fistula located in the center of the lateral wall trachea middle part of trachea. The presence of DM, the stent placement in the middle esophagus and presence of a mass invading the mediastinum were risk factors for fistula development in the present case. The length of the stent was shorter than 12 cm and had been fitted approximately 2 months earlier, and no ICI-related pseudoprogression was detected. After excluding differential diagnoses, it was concluded that the TEF may have developed as a side effect of the ICI treatment.

The development of ICI-induced fistula is thought to be a result of avascular necrosis or small vessel vasculitis developing into ischemia. It has been reported that the stent itself can cause tissue hyperplasia and inflammatory cell infiltration in patients with an esophageal stent, and that these factors in combination may lead to the development of fistula in patients with a stent undergoing ICI treatment. (6) TEF is diagnosed based on radiology and endoscopic procedures, and requires a multidisciplinary approach that includes interventional pulmonology, gastroenterology and thoracic surgery. Survival after a TEF diagnosis is usually less than 3 months. Comorbidities such as DM, airway infection, steroid use, and the presence of a nasogastric tube increase the risk of TEF. The clinical course varies depending on the size and localization of the tracheoesophageal fistula, comorbidity and immunological status of the patient. (10) Our case had diabetes mellitus and a 4 cm fistula in the lateral wall of the central third of the trachea. A bilateral stent placement in both the esophagus and the trachea is recommended for treatment (1). As our patient had an esophagus stent, it was planned to apply a stent to the trachea, however the patient died from a sudden massive hemoptysis. Survival after the placement of an esophageal stent was 2 months in the patient, which was consistent with previous studies.

It should be kept in mind that a tracheoesophageal fistula may develop in the presence of such facilitating factors as mediastinal invasion, CRT prior to ICI treatment (which has recently gained popularity for the treatment of NSCLC in recent years), comorbidities such as DM, steroid therapy and mediastinal invasion. In patients with esophageal or tracheal stents, follow up should be taken in the treatment and follow-up of ICI in terms of the risk of fistula development.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - A.B., S.Y., M.A.Ö., M.A.K., L.A.; Planning and Design - S.Y., M.A.Ö., A.B., M.A.K., L.A.; Supervision - A.B., S.Y., M.A.Ö., M.A.K., L.A.; Funding - M.A.Ö., S.Y., A.B.; Materials - M.A.Ö., L.A., A.B.; Data Collection and/or Processing - L.A., M.A.Ö.; Analysis and/or Interpretation - L.A.; Literature Review - M.A.Ö.; Writing - A.B., M.A.Ö., L.A.; Critical Review - A.B.

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