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PD-1/PD-L1-negative tracheal mucoepidermoid carcinoma: A case report and systematic review of the literature

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ABSTRACT

Background: Tracheal mucoepidermoid carcinoma is a rare form of non-small cell lung carcinoma and is defined as a tumor characterized by a combination of squamous, mucus-secreting, and intermediate cell types. This carcinoma is usually located in the lobar or segmental bronchus. Currently, surgery is the preferred treatment for this disease, which includes pneumonectomy, lobectomy, and sleeve lobectomy. **Case presentation:** A 50-year-old Chinese male presented with cough, shortness of breath and hemoptysis, and the effect of antibiotic therapy was not good. Subsequently, the airway occupied lesion was found by chest CT, and he was transferred to our hospital for surgical resection. Histologically, the tumor contained squamous epidermal cells, mucoepidermoid cells and intermediate cells. Immunohistochemistrically, the tumor cells were positive for p63, CK5/6, CK7 and Ki67. However, the tumor is generally negative for TTF-1 and neuroendocrine markers. The patient had no recurrence 15 months after the surgery. **Conclusions:** We report a rare case of mucoepidermoid carcinoma in the distal trachea in which the surgery was difficult and could not be performed like a traditional pulmonary resection. We first provide a comprehensive description of airway management and anesthesia intubation. After surgery, we reviewed the literature and found that PD-1/PD-L1 detection had never been reported in tracheal mucoepidermoid carcinoma. Therefore, we studied the PD-1/PD-L1 pathway in this patient, and the results were negative, which may indicate that potential adjuvant therapy with immune checkpoint inhibitors (ICIs) is not useful in this case.

Keywords: mucoepidermoid carcinoma (MEC), tracheal mass, airway management, anesthesia intubation method, PD-1/PD-L1.

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Background

As a malignant neoplasm, the WHO named mucoepidermoid carcinoma (MEC) in 1990, and it was first described as a separate pathological entity by Stewart in 1945[1, 2]. MEC accounts for <10% of all tumors of the salivary glands and mainly occurs in the parotid glands and small salivary glands. MEC originating from the trachea and bronchus is very rare; it accounts for 0.1-0.2% of primary lung tumors and is more prevalent in females (approximately 1.5 times) than in males. The onset age of tracheal MEC is relatively young, with the median age at presentation being approximately 40 years old[1]. The clinical symptoms are mostly atypical and mainly manifested as cough, hemoptysis, pneumonia, wheezing, fever, chest pain and other symptoms and signs; MEC is easily misdiagnosed as endobronchial tuberculosis, bronchitis or asthma[1, 3]. Currently, surgery is the preferred treatment for this disease, but the choice of follow-up treatment is still uncertain. Immune checkpoint inhibitors against programmed death 1/programmed death ligand 1 (PD-1/PD-L1) have revolutionized the treatment of several solid tumors, and PD-L1 was reported to predict the response to immunotherapy[4, 5]; however, no studies have reported the expression of PD-1/PD-L1 in MECs. In this report, we describe the diagnostic, anesthetic, and surgical management of a MEC patient with negative PD-1/PD-L1 expression in the distal trachea.

Table 1. Preoperative and postoperative lung function test.

	preoperative			postoperative		
	Predict	Actual	Actual/Predict%	Predict	Actual	Actual/Predict%
FVC (L)	4.06	3.54	87.11	4.05	2.62	64.68
FEV1(L)	3.32	1.27	38.33	3.31	2.52	76.21
FEV1/FVC (%)	81.78	35.93	43.93	81.73	96.13	117.62
mef25 (l/s)	1.63	0.6	36.71	1.62	1.86	114.76
mef50 (l/s)	4.24	0.85	20	4.23	3.47	82.15
mef75 (l/s)	7.54	1.16	15.45	7.53	7.32	97.29
PEF (L/S)	8.22	1.73	21.03	8.2	7.43	90.57
MVV(L/min)	141.92	39.58	27.89	141.4	104.89	74.18

Notes: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; MEF75, MEF50, MEF25—maximum expiratory flow rates were evaluated at the usual intervals of 75%, 50% and 25% of exhaled forced vital capacity; PEF—peak expiratory flow; MVV, maximum ventilatory volume.

Table 2. Summary of the clinicopathological features and treatment of patients.

Characteristics	*N* (%), median (range)
Age (83 available) (years)	
≥18（44 available）	42.5（20-81）
<18（39 available）	9（2-17）
Sex (83 available)	
Male	53（63.9）
Female	30（36.1）
Smoking history (29 available)	
yes	13（44.8）
No	16（55.2）
Tumor location (63 available)	
Trachea (above the carina)	6（9.5）
main bronchi	27（42.9）
Lobar bronchi	21（33.3）
Segmental bronchi	8（12.7）
Interlobar pleura	1（1.6）
Tumor size (cm) (46 available)	3.19±1.77（0.7-8.2）
Pathology classification (62 available)	
low-grade	47（75.8）
high-grade	11（17.7）
Intermediate-grade	4（6.5）
treatment (80 available)	
surgical resection	66（82.5）
Therapeutic bronchoscopy	8（10.0）
video-assisted thoracic surgery	1（1.25）
Palliative chemotherapy and Radiotherapy	5（6.25）
Adjuvant chemotherapy (75 available)	
Yes	2（2.7）
No	73（97.3）
Outcome and follow-up (65 available)	
CR	56（86.2）
PR	3（4.6）
PD	6（9.2）

Notes: CR, complete response; PR, partial response; PD, progressive disease.

Case Presentation

Clinical History

A 50-year-old Chinese male complained of cough, shortness of breath and hemoptysis for 10 days. The situation did not improve with antibiotic therapy at a local hospital. He underwent chest computed tomography (CT), showing a polypoid tumor just above the main carina, and was transferred to our hospital. The patient was a smoker of 30 years, with an average of 20

cigarettes a day. No family history of malignancy was found. Physical examination demonstrated obvious retractions of the suprasternal, supraclavicular and intercostal regions.

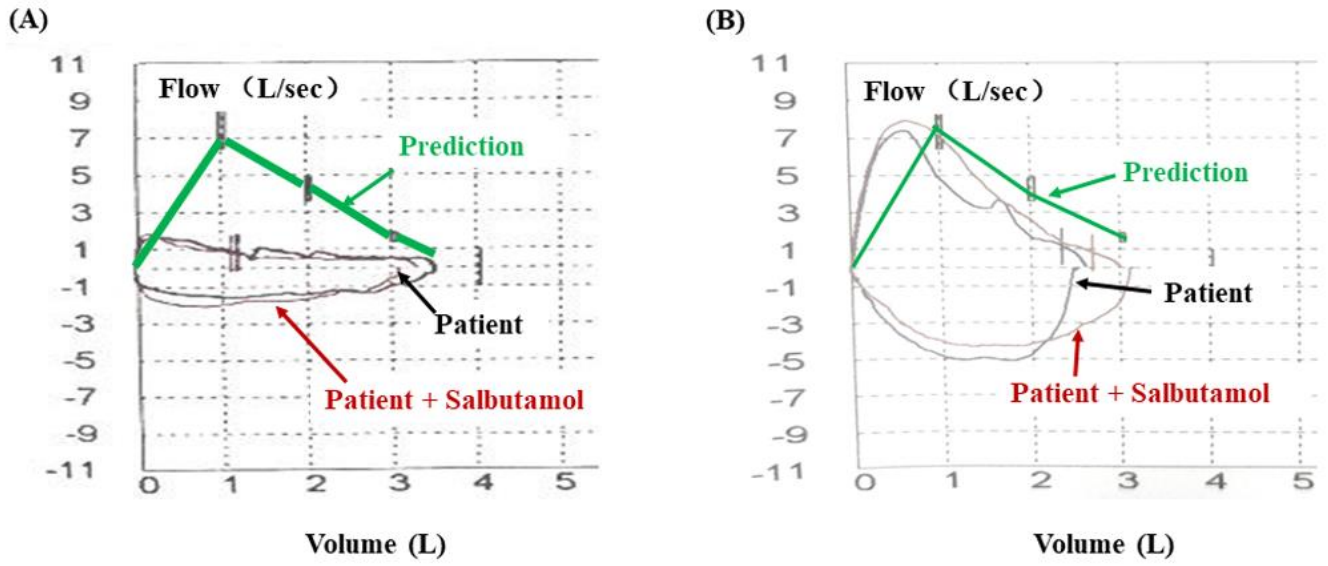

Figure 1. Preoperative and postoperative lung function test. **Notes: (A)** preoperatively, the F-V ring presents a characteristic platform shape, suggesting that inspiratory and expiratory flow is significantly limited; **(B**) postoperatively, pulmonary function indicates mild mixed ventilation dysfunction and normal small airway function.

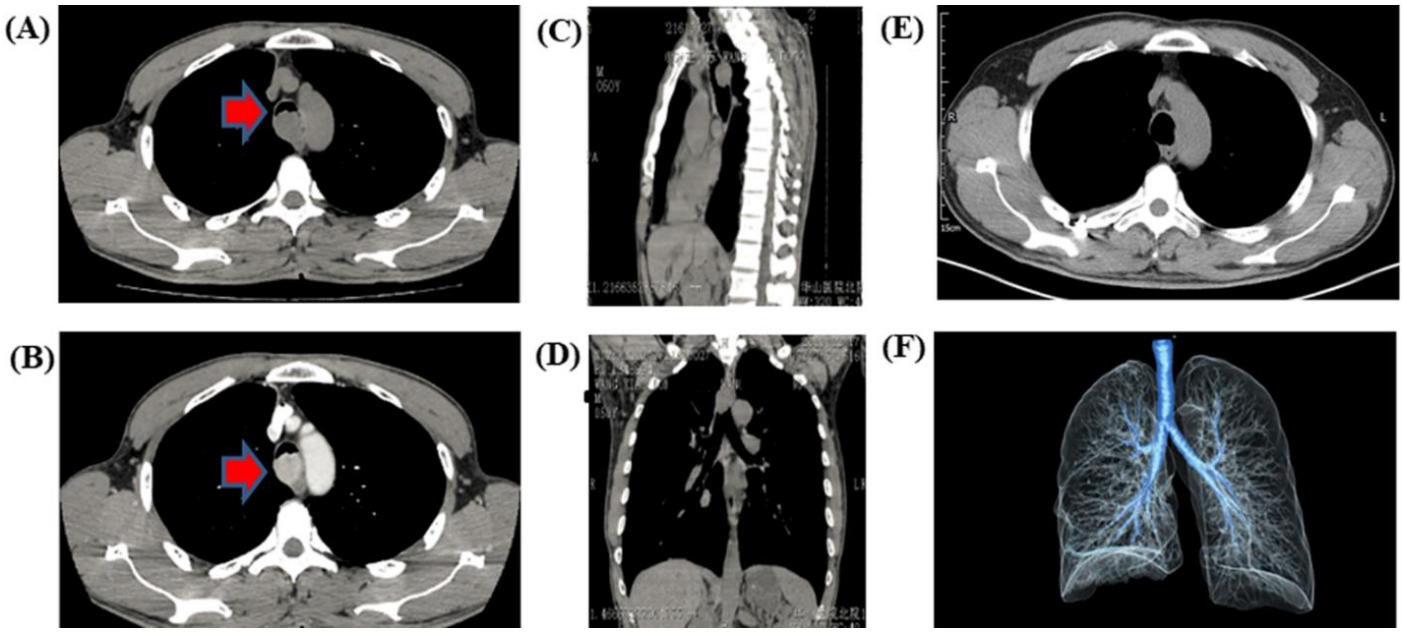

Figure 2. Chest CT demonstrating a polypoid endotracheal tumor. **Notes: (A)** (mediastinal window), **(B)** (enhanced CT), **(C)** (coronary position, 3D reconstruction) and **(D)** (sagittal position, 3D reconstruction) preoperative chest CT images showing tracheal obstruction by a lobulated heterogeneous enhancing soft tissue lesion; **(E)** and **(F)** postoperative chest CT images showing that the tracheal was well without a tumor.

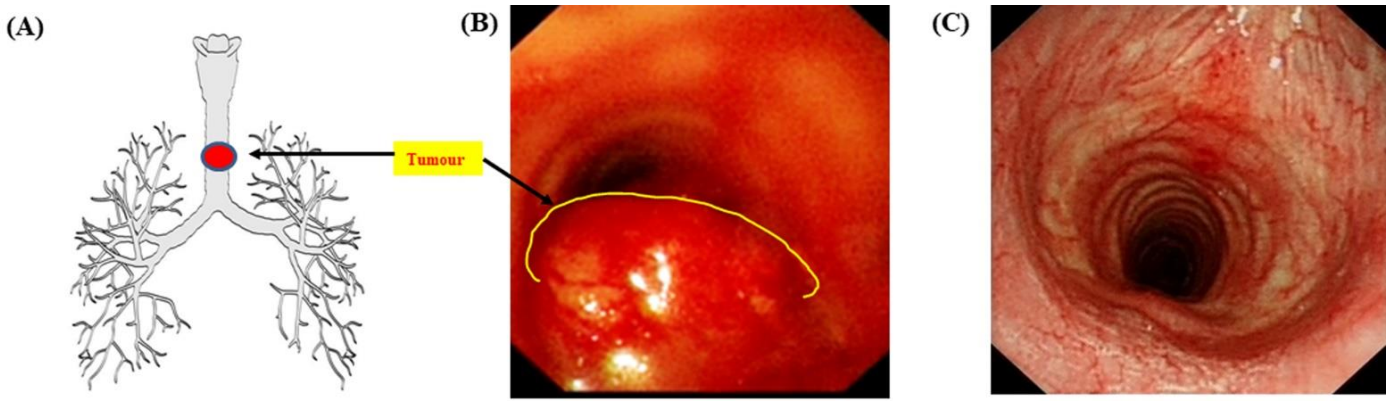

Figure 3. Bronchoscopic view of the tumor protruding into the trachea.

Notes: (A) the tracheal tree pattern; **(B)** preoperative bronchoscopic image showing the 2.2 cm tracheal tumor that occluded the distal trachea; **(C)** postoperative bronchoscopy.

Test results

Tumor markers were all normal, lung function showed flow limitation, and flattening was noted in both the inspiratory and expiratory limbs of the flow-volume loop (Table 1 and Figure 1A). Chest-enhanced CT found tracheal obstruction by a lobulated heterogeneous enhancing soft tissue measuring 2.2 cm, with suspected breakthrough of the airway wall, and no obvious enlarged lymph nodes in the mediastinum (Figure 2A-D). Flexible bronchoscopy (Figure 3A, 3B) was performed and revealed a mass protruding from the distal posterior tracheal wall 1 cm proximal to the carina. The tumor had a broad base, and its surface was not smooth and easily bled. A biopsy was performed at the local site of the lesion, and the bronchoscopy results indicated papillary tumor and mild cell dysplasia.

Operation and Pathological Examination Results

On December 19, 2019, the patient was referred for surgical management and underwent right posterolateral thoracotomy resection. Airway management was relatively difficult, and endotracheal intubation (via the mouth) was performed below the level of the lesion under general anesthesia. The trachea was incised at the lower edge of the tumor after careful separation, the endotracheal tube was withdrawn above the lesion and replaced by an auxiliary tube inserted into the distal left bronchus of the lesion to maintain adequate ventilation, the tumor segment trachea was resected along the upper and lower edges, and a frozen section verified that the tracheal margins were free of the tumor. End-to-end anastomosis was performed on the posterior wall of the trachea, the auxiliary tube was withdrawn, and the anastomosis on the anterior wall was completed without difficulty, as shown in Figures 4-5. Grossly, the tumor was an exophytic endobronchial circumscribed mass approximately 3 cm long and scaly with a hard white matter that blocked approximately 70% of the lumen. Histological staining showed squamous epidermal cells, mucoepidermoid cells and intermediate cells (Figure 6A-D). Immunohistochemical staining showed CK (+), P63 (+), HCK (+), ViM (-), LCA (-), CD56 (-), TTF-1 (-), P53 (+), SY (-), NapsinA (-), S100 (-), Ki67 (5%+), Calponin (-), CK5/6 (+), CK7 (small amount +), and PAS (-) 7-9: CK (-). The PD-1 and PD-L1 tests were negative (Figure 7). A

diagnosis of primary tracheal MEC was finally determined, and no mediastinal lymph node involvement was observed.

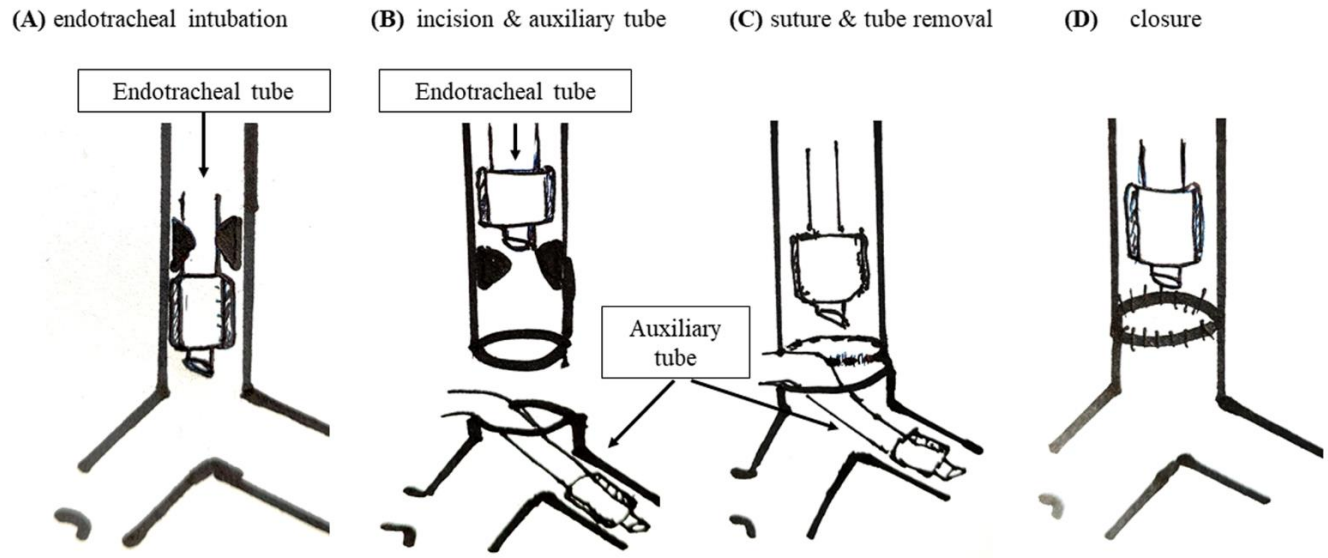

Figure 4. Anesthesia management, tracheal resection and reconstruction.**Notes: (A)** endotracheal intubation (via mouth) was performed below the level of the lesion; **(B)** after tracheal resection, an auxiliary tube was inserted into the left bronchus distal to the lesion; **(C)** primary anastomosis; **(D)** after anastomosis, mechanical ventilation was maintained through an endotracheal tube.

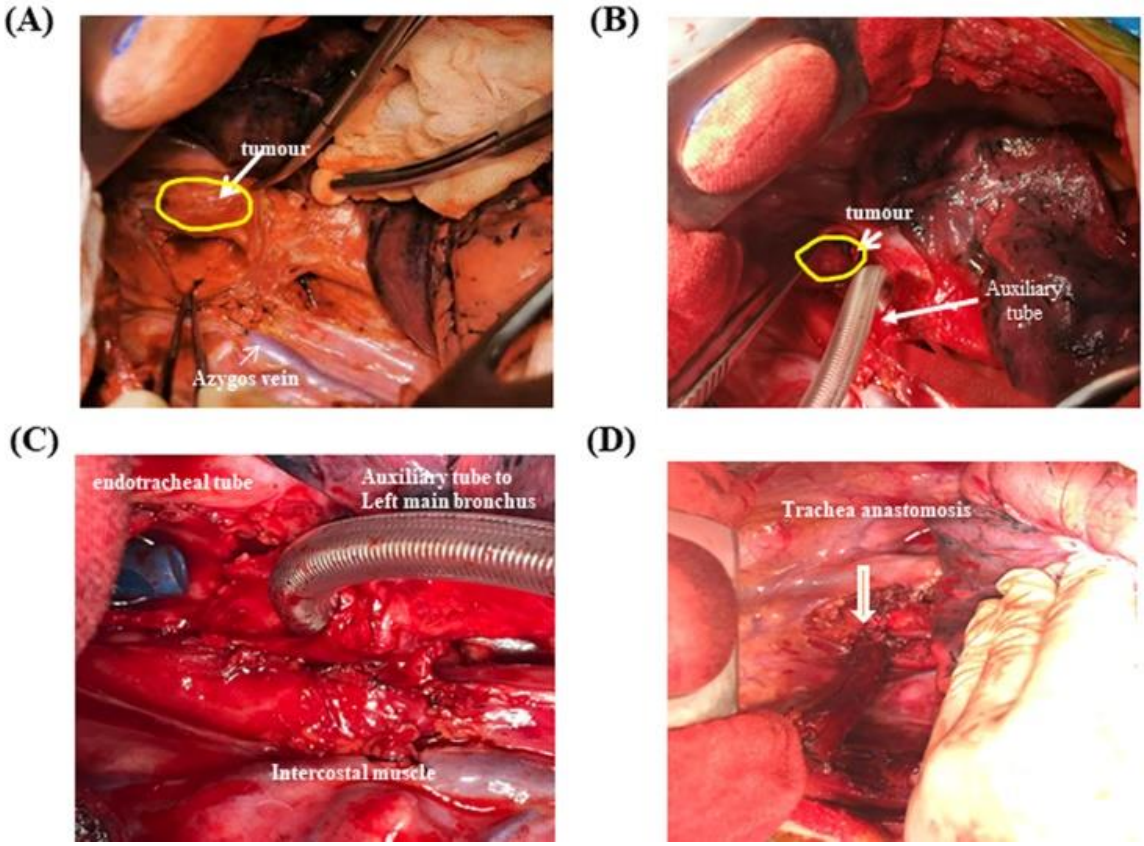

Figure 5. Tracheal resection and reconstruction.**Notes: (A)** exposure of the trachea; **(B)** intubation of the left bronchus with an auxiliary tube, the tumor is exposed in the trachea; **(C)** tumor resection and suture of the posterior wall of the broken end of the trachea; **(D)** free intercostal muscle and

pedicel muscle flap to prevent anastomotic leakage.

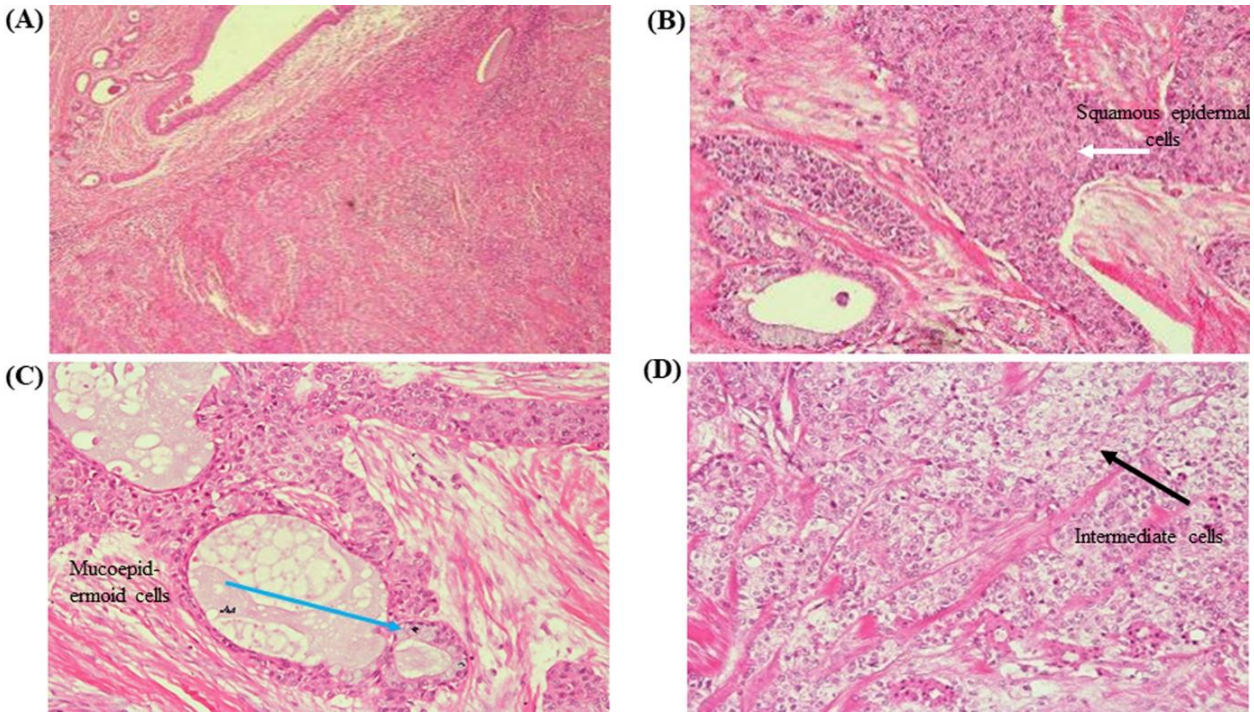

Figure 6. Pathology of the tracheal resection. **Notes: (A)** HE 40× mucoepidermoid carcinoma; **(B)** HE 100×; **(C)** HE 200×; **(D)** HE 200×; squamous epidermal cell (white arrow), mucoepidermoid cell (blue arrow), intermediate cell (black arrow).

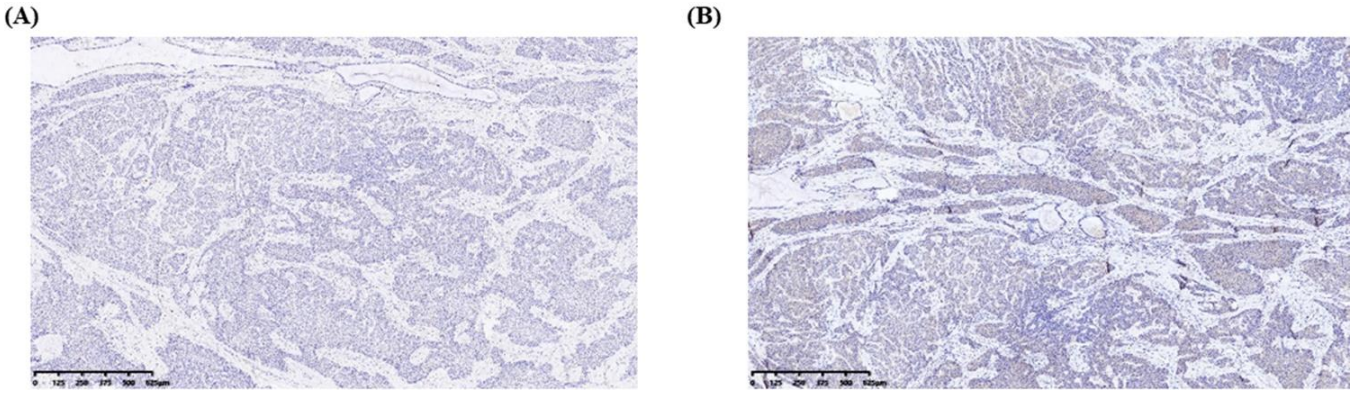

Figure 7. PD-1/PD-L1-negative tracheobronchial mucoepidermoid carcinoma. **Notes: (A)** PD-1 40×; **(B)** PD-L1 40×.

Post-Operative follow-up

Postoperative recovery was satisfactory, and the outcome and surgical efficacy were investigated after 15 months of follow-up. Six months after surgery, activity endurance and pulmonary function (Table 1 and Figure 1B) were significantly improved, and no discomfort was reported. Chest CT (Figure 2E, 2F) and bronchoscopy (Figure 3C) indicated that the trachea was unobstructed and that there was no tumor growth. At the last telephone follow-up in Nov 19, 2021, the patient was well without any signs or symptoms of recurrence.

Discussion and Conclusions

The incidence of tracheal MEC is low. While still

controversial, MEC is generally believed to originate from the ductal epithelium of the submucosal glands of the bronchus[6]. Because the tumor mostly occurs in the lobar or segmental bronchi and especially in the peripheral lungs [7], the early stage is asymptomatic, and a small number of patients were noted only during routine health examinations. As the tumor grows and blocks the bronchial lumen, the patient presents with clinical symptoms of airway obstruction, such as cough, sputum coughing and progressive shortness of breath, which are easily misdiagnosed as endobronchial tuberculosis, bronchitis or asthma [1, 3, 8]. The patient we reported had obvious symptoms because the tumor was large enough and located in the distal trachea.

CT scans and bronchoscopy represent the main diagnostic tools for this disease, but the misdiagnosis rate of bronchoscopy biopsy is relatively high. Hsieh et al. reported that in a retrospective study of 41 cases of pulmonary MEC, only 4 patients had an accurate preoperative diagnosis from bronchoscopic biopsy [9]., which may be related to factors such as brittle tumors that bleed easily and small or shallow samples. The diagnostic gold standard for MEC is histopathological examination. There is no single immunohistochemical stain that one can define as pathognomonic for MEC[1], but Roden AC et al. reported that MAML2 rearrangement studies might be helpful in the distinction of MEC from other epithelial lung malignancies [10]. In this case, the tumor shows positive staining with antibodies commonly used for squamous cell carcinoma, such as p63 and CK5/6. In addition, the tumor may also show mild positive staining for CK7 and Ki67; however, the tumor is generally negative for TTF-1 and neuroendocrine markers. All of these findings are consistent with previous reports[1, 11-13].

A literature search was performed using the PubMed database to determine the availability of all full-text articles on tracheal MEC in English before April 2021. In total, 73 articles involving 83 cases were identified (Table 2); there were only 6 cases of tracheal lesions, accounting for 9.5%, and the rest were all derived from bronchial lesions. Therefore, here we report the seventh case of trachea-derived MEC.

Treatment of tracheal MEC depends on its aggressiveness and the extent of its spread. Currently, surgical resection is considered the first treatment for this disease, which includes pneumonectomy, lobectomy, and sleeve lobectomy[6, 14]. Of the 6 cases of tracheal MEC we retrieved, 2 cases were due to worsening upper airway obstruction, and emergency rigid bronchoscopy followed by electrocautery snaring was performed to remove the bulk of the tumor [15, 16]. One patient injured the azygous vein and a branch from the right pulmonary artery leading to massive intratracheal bleeding, and an emergency sternotomy was performed. One patient received bronchoscopic polypectomy using a snare to relieve symptoms[17]. The other patient was a woman at 27 weeks of gestation, and she was treated by therapeutic bronchoscopy with argon plasma coagulation [18]. Only 2 patients underwent surgical resection, but no records of anesthesia or surgical procedures were reported [19, 20]. In this report, we first provide a comprehensive description of airway management and anesthesia intubation because this case highlights the challenges with anesthesia and surgical interventions of large airways. Most cases have no recurrence in long-term clinical follow-up after complete tumor resection. Chemotherapy was used for patients with metastasis or inoperable evaluation. Some scholars also treat this disease with Epidermal Growth Factor

Receptor (EGFR) inhibitors, suggesting that effective remission, recurrence delay and survival were achieved via EGFR inhibition [3, 21].

Important prognostic factors for MEC include histological type, TNM stage, radiation uptake and age[22]. Compared with high-grade MEC, low-grade MEC has a very good 5-year survival rate [23]. Fortunately, low grade MEC is dominant, accounting for 75.8% of the data in our statistics. Due to the rarity of tracheal MEC, there is no standardized approach to postoperative treatment. The majority of low-grade MEC cases were followed up regularly, while a few high-grade MEC cases were followed up with subsequent adjuvant chemotherapy or radiotherapy.

Immunotherapy, especially the use of immune checkpoint inhibitors (programmed death 1/programmed death ligand 1), has revolutionized the management of several different cancer types in recent years, and PD-L1 was reported to predict the response to immunotherapy [4, 5]. In normal adult tissue, PD-L1 is constitutively expressed in normal placental trophoblasts as well as choriocarcinomas and trophoblastic components of germ cell tumors. Additionally, some neoplastic cells, such as squamous cell carcinoma of various sites, frequently express PD-L1[24]. PD-L1 is only rarely expressed in adenocarcinoma cells and is not expressed in pulmonary schwannoma [24, 25]. Normal lung parenchyma lacks PD-L1 expression, while lung carcinomas express varying levels of PD-L1[24, 26]; however, PD-1/PD-L1 expression has never been examined in tracheal MECs. Given the recent use of immune checkpoint inhibitors, as well as different levels of PD-1/PD-L1 expression in different organs, we investigated the PD-1/PD-L1 pathway in this patient. Surprisingly, this tumor was negative for PD-1/PD L1 immunoreactivity, which may indicate that potential adjuvant treatment with immune checkpoint inhibitors would not have been useful in this particular case. Of course, our sample data are too small, and checkpoint inhibitors remain to be tested in large clinical samples.

In summary, we present a case of PD-1/PD-L1-negative tracheal MEC, and describe anesthesia intubation and surgical procedures in detail. This kind of pulmonary malignant tumor is prone to misdiagnosis and missed diagnosis because of atypical clinical symptoms in the early stage. CT and bronchoscopy should be comprehensively applied to identify airway lesions, and patients should be treated as soon as possible.

Acknowledgements

None.

Abbreviations

MEC mucoepidermoid carcinoma

CT computed tomography

PD-1/PD-L1 programmed death 1/programmed death ligand 1

EGFR Epidermal Growth Factor Receptor

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Huashan North Hospital Affiliated to Fudan University. The patient gave consent to participate.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

All the original data supporting our research are described in this article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study conception and design. Yingying Liu and Jian Guo: data collection and manuscript writing. Ji Chen, Hai xia Li and Zeng tao Wang: result interpretation, literature search, and manuscript writing. Jie Liu: manuscript writing, proof reading. Yi Gong: mentoring of project, manuscript writing, and proof reading. All authors read and approved the final manuscript.

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