Adenoid Cystic Carcinoma of Esophagus with Lung Metastasis: Case Report

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Adenoid cystic carcinoma (ACC) is a malignant tumor originating in the salivary glands. It most commonly affects the salivary and lacrimal glands, with less frequent occurrences in the esophagus. Esophageal ACC (EACC) typically manifests in the middle or lower parts of the esophagus, with exceedingly rare instances in the upper part. Lung metastasis in EACC is uncommon, and understanding its clinical features and treatment strategies remains challenging. In this study, we present a case of ACC originating in the upper esophagus with lung metastasis. The patient, a middle-aged female, was admitted to the Department of Respiratory and Critical Care Medicine due to an esophageal mass discovered during physical examination that had been present for 4.5 years, along with a newly identified pulmonary nodule for 2 weeks. An X-ray barium meal revealed the presence of a benign esophageal cervical mass. Gastroscopy revealed elevated lesions below the esophageal inlet, and a pathological biopsy confirmed the diagnosis of EACC. The aim of this case report is to enhance understanding of this rare condition and improve clinicians' awareness of the disease. By providing details of the patient's diagnosis, clinical presentation, imaging features and pathological features, we aim to improve diagnostic accuracy and clinical management of similar cases in the future.

Keywords: esophageal cancer; adenoid cystic carcinoma; lung metastasis

Introduction

Adenoid cystic carcinoma (ACC) is a malignant tumor originating in the salivary glands. It is most commonly found in the salivary and lacrimal glands, with less frequent occurrences in the esophagus. Esophageal ACC (EACC) typically manifests in the middle part of the esophagus, followed by the lower part [1], while occurrences in the upper part are extremely rare. Lung metastasis in EACC is uncommon, and understanding its clinical features and treatment strategies remains challenging.

This report presents a case of ACC originating in the upper esophagus and presenting with lung metastasis. The aim is to enhance understanding of this rare condition and improve clinicians' cognitive level and diagnostic ability regarding the disease.

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Due to the extremely low incidence of ACC, there are limited relevant reports both domestically and internationally. The majority of existing literature comprises case reports, indicating a lack of exploration at the molecular level, resulting in unclear specific pathogenesis and etiology. Current research has identified associations between smoking, alcoholism, hiatal hernia, and obesity with a significant proportion of reflux esophagitis, which serves as a high-risk factor for the development of EACC [2].

Numerous studies have indicated a close relationship between the *C-KIT* gene and the etiology, diagnosis, treatment, and prognosis of salivary gland ACC. Adenoid cystic carcinoma is characterized by a low degree of malignancy and slow progression, typically presenting insidiously without obvious symptoms in the early stages. As the tumor advances, initial symptoms of EACC often mimic those of esophageal squamous cell carcinoma (ESCC), frequently manifesting as progressive dysphagia, epigastric pain, or discomfort after eating [3].

Materials and Results

A 49-year-old female patient was admitted to the Department of Respiratory and Critical Care Medicine on May 10, 2023, due to an esophageal mass discovered during a physical examination, which had been present for 4.5 years,

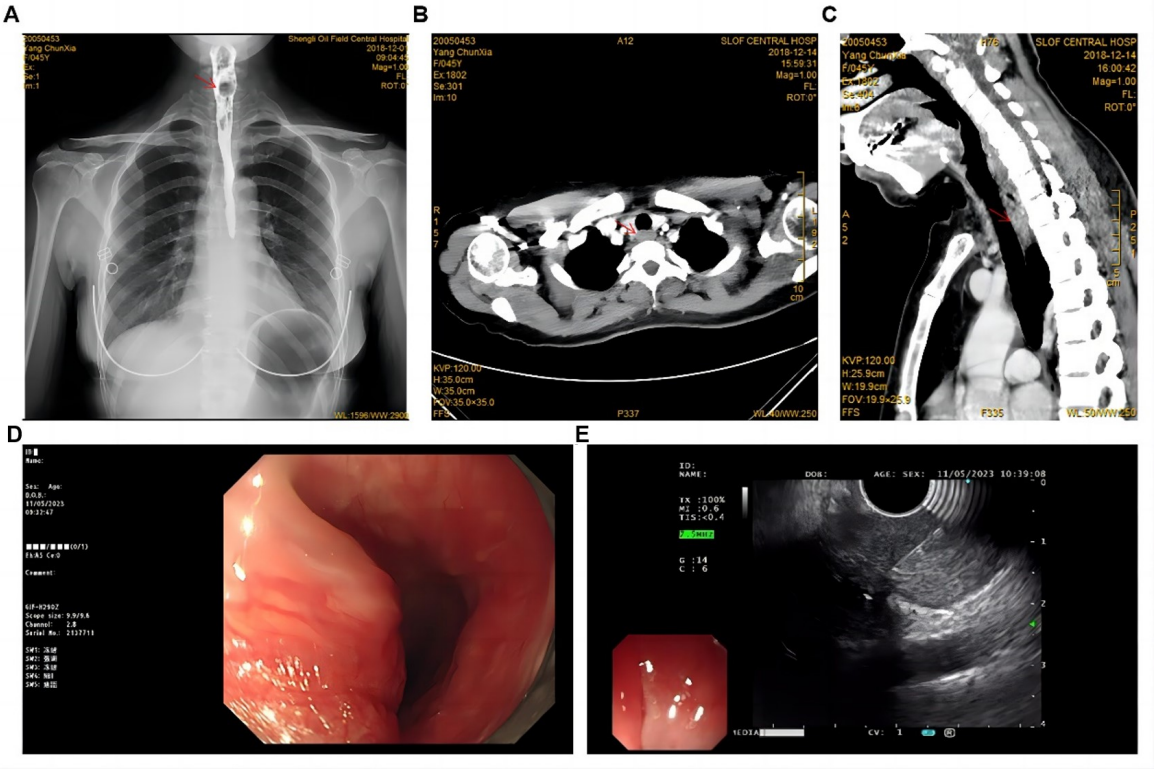

Fig. 1. Imaging and endoscopy results. (A) An oval filling defect measuring approximately 2.6 × 1.8 cm was observed in the cervical segment of the esophagus, characterized by a smooth margin, clear boundary, and soft local wall. There was good dilatation with a slightly obstructed passage of barium (arrow). (B,C) Localized thickening of the right wall of the cervical segment of the esophagus, measuring 2–3 cm, was noted. This thickening exhibited significant enhancement on contrast-enhanced scans compared to the contralateral esophageal wall, with a computed tomography (CT) value ranging from approximately 83 to 106 HU. The plain scan showed unclear findings, along with eccentric narrowing of the esophageal lumen (arrow). (D,E) Elevated lesions were observed below the esophageal inlet, characterized by a mucosal surface less smooth than normal. Ultrasound imaging revealed substantial thickening of the esophageal mucosa, measuring approximately 2 cm in thickness with a clear boundary.

and a pulmonary nodule for 2 weeks. On December 1, 2018, the patient underwent an upper gastrointestinal barium meal examination, which suggested a diagnosis of a benign esophageal cervical mass, with a high likelihood of leiomyoma (Fig. 1A). Subsequently, a contrast-enhanced computed tomography (CT) examination of the chest revealed localized thickening of the right cervical esophagus wall, interpreted as a mass (Fig. 1B,C). Previous gastroscopy conducted outside the hospital showed no apparent abnormalities, leading the patient to seek treatment for benign esophageal conditions at the China Medical Science Cancer Hospital, without any specialized intervention. Following this, the patient underwent regular chest CT re-evaluations without experiencing any notable discomfort. A contrast-enhanced chest CT performed two weeks ago yielded the following findings: (1) thickening of the cervical esophagus wall, considered as a mass; and (2) multiple nodules in both lungs, with the possibility of external metastasis not being ruled out.

On May 10, 2023, a whole-body positron emission tomography (PET)–CT examination was conducted. Considering the possibility of space-occupying lesions in the cervical esophagus and multiple metastases in both lungs (Fig. 2A–D), it was recommended to confirm the diagnosis through a combination of biopsy pathology to rule out other diseases. The patient reported no cough, expectoration, fever, night sweats, chest pain, hemoptysis, chest tightness, suffocation, choking sensation when eating, acid reflux, heartburn, nausea, vomiting, or any other discomfort, and was admitted for further diagnosis and treatment. Medical history, family history, personal history, marriage, and childbearing history were unremarkable.

Upon admission, the patient's physical examination revealed the following: temperature = 36.3 °C, heart rate = 72 beats per minute, respiratory rate = 18 breaths per minute, and blood pressure = 110/70 mmHg (1 mmHg = 0.133 kPa). The patient was fully conscious with a good mental state, no enlargement of superficial lymph nodes, clear breath sounds in both lungs, and no audible dry or moist rales.

The cardiac and abdominal examinations revealed no positive signs, and there was no edema present in either of the lower limbs. The preliminary diagnosis upon admission

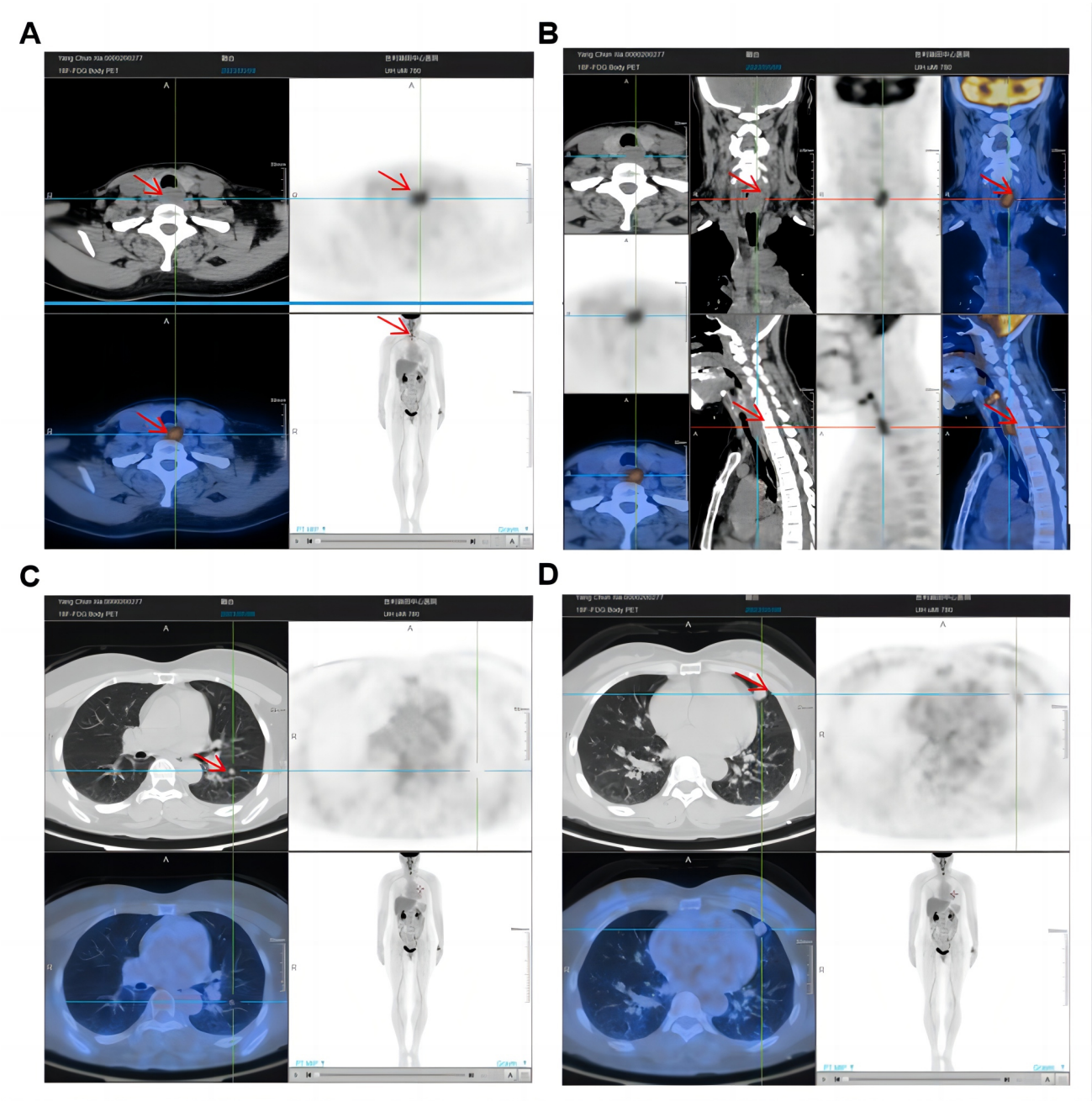

Fig. 2. Positron emission tomography–computed tomography (PET–CT) examination results. (A,B) The systemic PET–CT revealed significant thickening of the cervical esophagus wall, accompanied by abnormal glucose metabolism, predominantly affecting the posterior wall. Space-occupying lesions in the cervical esophagus segment were suspected (arrow). (C,D) On systemic PET–CT imaging, multiple solid nodules of various sizes were detected in both lungs, with some exhibiting slightly increased glucose metabolism. The largest nodule, measuring approximately 16.0 × 15.0 mm, was located in the lingual segment of the left lung. It demonstrated a maximum standardized uptake volume of approximately 2.4, with lobulation at the edge, raising the suspicion of metastases (arrow).

was as follows: esophageal space-occupying lesion, suggestive of an esophageal malignant tumor with a high likelihood of bilateral lung metastasis.

The post-admission auxiliary examination results were as follows: The blood routine revealed four coagulation items along with D-dimer levels. Additionally, arterial blood gas analysis, goodness-of-fit test, galactomannan test, tuberculosis infection T cell test (T-SPOT), antinuclear antibody, and extractable nuclear antigen zymogram results were negative. Tumor markers, including carcinoembryonic antigen (CEA), neuron-specific enolase, CYFRA21-1, CA125, and CA199, as well as urine and stool routine tests, were within normal ranges.

On May 12, 2023, electronic gastroscopy was conducted, revealing elevated lesions below the esophageal inlet. The mucosal surface appeared less smooth than normal, and

ultrasound scanning indicated a significantly thickened esophageal mucosa, approximately 2 cm thick, with clear borders (Fig. 1D,E). Color Doppler flow imaging (CDFI) showed a small number of blood flow signals, and the muscularis propria of the esophagus appeared continuous and intact, as was the extramural adjacent thyroid tissue.

Subsequently, an endoscopic ultrasound-guided fine-needle aspiration biopsy was performed, using a 22G puncture needle to biopsy the mucosal mass at the esophageal inlet to obtain cytological and histological samples. Rapid on-site evaluation was also conducted. Microscopic examination revealed cancer cells arranged in a spherical structure with translucent myxoid stromal spheres within the cell mass, suggesting the possibility of ACC (Fig. 3A,B).

Pathological findings obtained on May 15, 2023, showed an extremely small number of tumor cells arranged in a cribriform pattern in the esophageal puncture tissue, with basophilic myxoid material observed in the cribriform foramen (Fig. 3C,D).

The immunohistochemical results were as follows: broad-spectrum CK and CK7 were positive (+), Ki-67 was positive (+, 30%), leukocyte common antigen was negative (-), P40 was positive (+), P63 was positive (+), S-100 was negative (-), CD117 was positive (+), epithelial membrane antigen (EMA) was negative (-), and P53 was wild-type (Fig. 3E–J). Special staining with periodic acid-Schiff (PAS) was positive (+) (Fig. 3K).

Combining the histological morphology with the immunohistochemical findings, the results were consistent with ACC. The pathological diagnosis was EACC.

On May 16, 2023, a CT-guided needle biopsy of the pulmonary nodules was conducted, yielding pathological results consistent with ACC. Consequently, the patient's final definitive diagnosis was EACC with bilateral lung metastases. Subsequently, the patient opted not to continue hospitalization at this facility and was transferred to a higher-level hospital for further management.

Discussion

Esophageal ACC is believed to originate from the esophageal glands. It typically manifests around the age of 60, with a male-to-female ratio of approximately 3.4:1. The tumor commonly develops in the middle segment of the esophagus and rarely in the upper segment [1].

However, in the present case, the patient was a middle-aged woman, and the lesion was situated in the upper esophagus. This differs from the reported age and site preferences documented in the literature, making the incidence rate rare in clinical practice [3].

Adenoid cystic carcinoma is characterized by a low degree of malignancy and slow progression. Typically, the tumor has an insidious onset with no obvious symptoms in the early stages. As the tumor progresses, initial symptoms of EACC often resemble those of ESCC, including progressive dysphagia, epigastric pain, or discomfort after eating [4]. However, in this particular case, the patient did not experience dysphagia, epigastric pain, or discomfort after eating. This was further confirmed through gastroscopy and endoscopic ultrasonography, which were conducted following the chest CT findings.

The diagnosis of EACC primarily relies on the results of pathological and immunohistochemical examinations. The lesion's location is determined through interventional surgical procedures such as endoscopic narrow-band imaging and endoscopic ultrasonography, which also facilitate the collection of pathological tissue samples. However, endoscopic biopsy may carry a risk of missed diagnosis for esophageal malignancies due to the limited amount of tissue obtained. The main reasons for missed diagnoses include insignificant early lesions, localization within the submucosa, and false-negative biopsy sampling results. Additionally, EACC is frequently misdiagnosed endoscopically as other lesions such as ESCC or esophageal leiomyoma, with a misdiagnosis rate as high as 78.4% [5]. In many cases, the disease has already progressed to an advanced stage by the time of definitive diagnosis, as was observed in the present report.

The most common endoscopic presentation of tumors in EACC is bulging (58.6%), followed by ulceration (24.1%) [6]. In the present case, gastroscopy was performed after the onset of the disease, but no signs of malignant tumors were detected. Consequently, the patient was followed up based on presumed benign esophageal lesions, leading to a missed diagnosis and misdiagnosis. The patient's tumor exhibited mucosal bulging, aligning with reports in the literature.

The primary pathological features of EACC include: (1) The tumor typically presents as a solid nodule, with an average diameter of approximately 3 cm. It appears greyish-white, slightly firm, lacks an obvious capsule, and is well-defined with predominantly infiltrative growth. (2) Microscopically, the tumor is composed of glandular epithelial cells and myoepithelial cells.

Histologically, ACC is classified into three main types: cribriform, tubular, and solid. The most common type, cribriform, is characterized by lacunae lined with glandular epithelial cells and surrounded by myoepithelial cells. These cribriform pores resemble pseudo-glandular cavities, varying in size, often filled with eosinophilic PAS staining-positive material or granular basophilic myxoid material.

Immunophenotyping studies have revealed that glandular epithelial cells express EMA, CEA, and CK7, while myoepithelial cells express smooth muscle actin, S100, CK5/6, P63, P40, and calponin. Additionally, CD117 may be expressed in some glandular epithelial and myoepithelial cells.

In the present case, microscopic findings indicated typical adenoid cystic carcinoma, with tumor cells arranged in a cribriform pattern comprising glandular epithelium and myoepithelium at the base, with cribriform pores containing

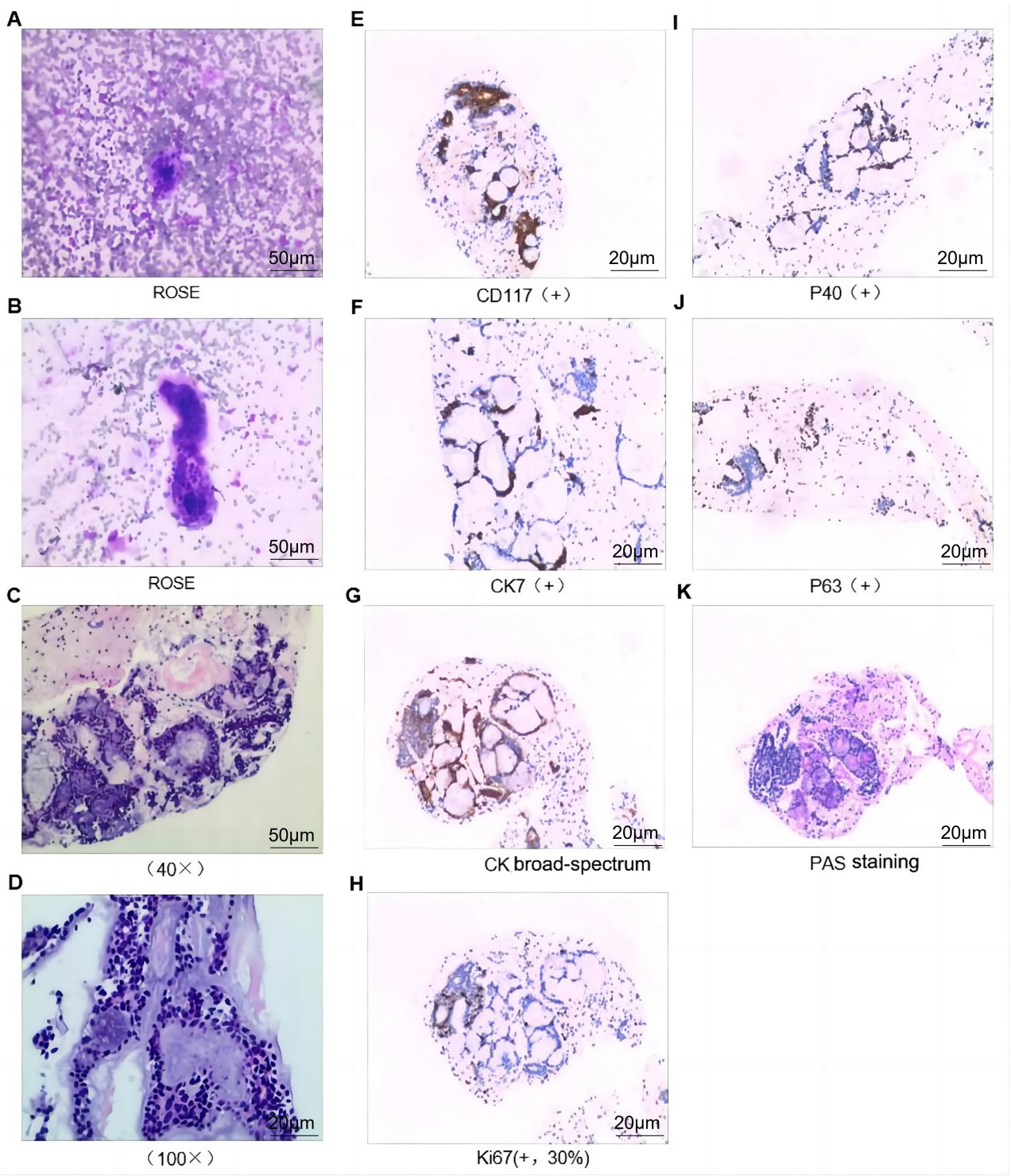

Fig. 3. Pathological Results. (A,B) Cells were distributed in small clusters, nuclei were round, uniform in size and hyperchromatic, cytoplasm was lightly stained, spindle cells were observed at the edge, and myxoid material was faintly observable in the lumen (magnification: 40×). (C,D) Oesophagus puncture histopathology: tumours were cribriform at low magnification, characterised by tumour cell nests in cylindrical microcystic systems, cysts were filled with clear or basophilic myxoid material, cells were divided into ductal cells and myoepithelial cells at high magnification, nuclei were hyperchromatic or angulated, and cytoplasm was often transparent. (E) CD117 expression was positive in the tumour tissues (magnification: 100×). (F) CK7 expression was positive in the tumour tissues (magnification: 100×). (G) CK expression was positive in the tumour tissues (magnification: 100×). (H) Ki-67 expression was positive in the tumour tissues (magnification: 100×). (I) P40 expression was positive in the tumour tissues (magnification: 100×). (J) P63 expression was positive in the tumour tissues (magnification: 100×). (K) Periodic acid-Schiff (PAS) staining was positive (magnification: 100×).

basophilic myxoid material. Furthermore, immunohistochemical analysis showed positive staining for CK7, P63, and CD117, consistent with findings reported in the literature.

Adenoid cystic carcinoma is a distinctive malignant tumor that requires differentiation from basal-like squamous cell carcinoma (SCC), neuroendocrine tumors, poorly differentiated SCC, and mucoepidermoid carcinoma. Its principal distinguishing features lie in the characteristics of tumor cells and immunophenotype.

Given the rarity of EACC, there is a notable scarcity of large-scale and systematic data regarding its treatment in the literature. The disease's high malignancy underscores the importance of radical surgical resection as the current preferred treatment option. However, evaluating the impact of postoperative adjuvant therapy (chemotherapy and radiotherapy) on patient survival poses challenges. Additionally, the efficacy of chemotherapy in patients with advanced disease remains uncertain due to poor sensitivity [1].

Molecular targeted drug therapy has emerged gradually in ACC treatment; however, its application is currently limited to ongoing and completed clinical trials, and has not garnered approval from the US Food and Drug Administration. Jensen *et al*. [7] documented a case in which a patient with EACC achieved remission following treatment with radiotherapy and cetuximab. Nonetheless, the quest for more effective treatment modalities for this disease remains ongoing.

In one instance, a patient developed bilateral lung metastases without surgical indications, prompting the administration of chemoradiotherapy in an effort to determine the optimal treatment regimen.

Although ACC generally carries a favorable prognosis, boasting a 5-year survival rate of 90.34%, a 10-year survival rate of 79.88%, and a 15-year survival rate of 69.22% [8], EACC presents a different clinical picture. This variant is more prone to lymph node metastasis and distant metastasis compared to other cancer types. The incidence of distant organ metastasis surpasses that of lymph node involvement, with frequent dissemination to the lungs, bones, brain, and liver [1], significantly impacting prognosis.

Upon clinical diagnosis, the 1-year survival rate dwindles to 23%, with an average survival period of approximately 7 months. However, surgical resection marginally improves the outlook, extending the mean survival to around 9 months [9].

In the current case, the patient presented with space-occupying lesions in the cervical segment of the esophagus persisting for over 54 months, coupled with bilateral lung metastases, indicating a short-estimated survival time. Follow-up procedures are currently underway.

Conclusion

In summary, EACC represents a relatively uncommon malignant tumor of the digestive system that often elicits challenges in diagnosis, including misdiagnosis and overlooked detection. Pathological and immunohistochemical examinations serve as the cornerstone for accurate diagnosis. Early identification proves pivotal in assessing the patient's condition and determining appropriate treatment, thereby enhancing clinical prognosis to some extent. This paper aims to enhance understanding of this tumor by presenting a rare case of EACC with lung metastasis.

Availability of Data and Materials

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding authors.

Author Contributions

LJT and JJS conceived of the study, and JJG, CW, SLZ, JMZ and XYW participated in its design and data analysis and statistics and JJG & CW helped to draft the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Shengli Oilfield Central Hospital (Q/ZXYY-ZY-YWB-LL202385). Written informed consent was obtained from the participant.

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Conflict of Interest

The authors declare no conflict of interest.

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