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Rapid metastasis of stage IA primary pulmonary high-grade mucoepidermoid carcinoma with a cystic airspace: a case report and reflection

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Abstract

Primary pulmonary high-grade mucoepidermoid carcinoma (MEC) with a cystic airspace is uncommon, and early metastasis is extremely rare. In such cases, however, it is clinically important for clinicians to consider whether the tumor has spread to the lymph nodes through the cystic airspace. A 77-year-old man presented to our hospital with cough and hemoptysis. Chest computed tomography showed a 25-mm-diameter mass with a cystic airspace located in the upper lobe of the left lung. The possibility of malignancy was considered. Without a definitive preoperative diagnosis, left upper lobectomy and mediastinal lymphadenectomy were performed. Histopathological examination revealed the typical histological characteristics of high-grade MEC (stage IA) and no lymph node metastasis. However, lymph node metastasis was found 6 months after surgical resection, and radiochemotherapy was performed. The patient developed widespread metastatic disease 4 months following completion of radiochemotherapy and died 2 months later. Primary pulmonary MEC with a cystic airspace is a rare malignant disease with uncommon imaging findings. Complete surgical resection is the main treatment method for

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high-grade MEC. In this case, we hypothesize that early metastasis was caused by seeding of tumor cells through the cystic airspace.

Keywords
Pulmonary mucoepidermoid carcinoma, cystic airspace, early-stage, metastasis, surgical resection, case report

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Introduction

Pulmonary mucoepidermoid carcinoma (MEC) is rare, accounting for only 0.1% to 0.2% of all pulmonary cancers.[1] MEC is a salivary gland tumor that originates from the submucosal glands of the tracheobronchial tree. It is divided into high-grade MEC and low-grade MEC. Low-grade MEC predominantly consists of glandular elements and mucus-secreting cells, whereas high-grade MEC consists largely of sheets or nests of squamoid and intermediate cells intermixed with smaller populations of mucus-secreting cells. MEC was first reported by Smetana et al.[2] in 1952. It shows an equal sex distribution with a slight predilection for men, and the age at onset ranges from 3 to 78 years with 50% of tumors occurring in individuals <30 years of age. Most patients present in the third and fourth decades of life.[1] Some reports have indicated that good results can be obtained by complete removal of low-grade MEC. However, high-grade MEC is a more aggressive malignancy with a poorer outcome. Positron emission tomography/computed tomography (PET/CT) appears to be a useful preoperative imaging modality for predicting the tumor grade, nodal stage, and postoperative prognosis. Patients with a maximum standardized uptake value of >6.5 are more likely to have a high-grade tumor, lymph node metastasis, and cancer recurrence.[3] Surgery is an appropriate treatment choice for patients with MEC if the lesion is resectable. We herein report a case of pulmonary MEC with a cystic airspace that exhibited early metastasis.

Case presentation

The reporting of this study conforms to the CARE guidelines.[4]

A 77-year-old man presented with an approximately 2-week history of cough and hemoptysis. He had smoked 20 cigarettes per day for 50 years. Physical examination revealed no abnormal signs in either lung. No significantly abnormal values were detected in the blood count or in the serum and biochemical data. Chest CT revealed a 25-mm-diameter mass with a cystic airspace in the upper lobe of the left lung (Figure 1 (a)). Bronchoscopy showed no abnormalities in the trachea or bronchi. Whole-body bone emission CT was normal. Brain CT showed senile encephalatrophy. Although diagnostic PET/CT would have been helpful for preoperative staging, the patient declined a PET/CT examination because of cost.

The patient underwent left upper lobectomy and mediastinal lymphadenectomy of the lymph nodes in groups 4, 5, 7, 10, 11, 12, 13, and 14. Histopathological examination showed that the resected tumor contained atypical cells with hyperchromatic

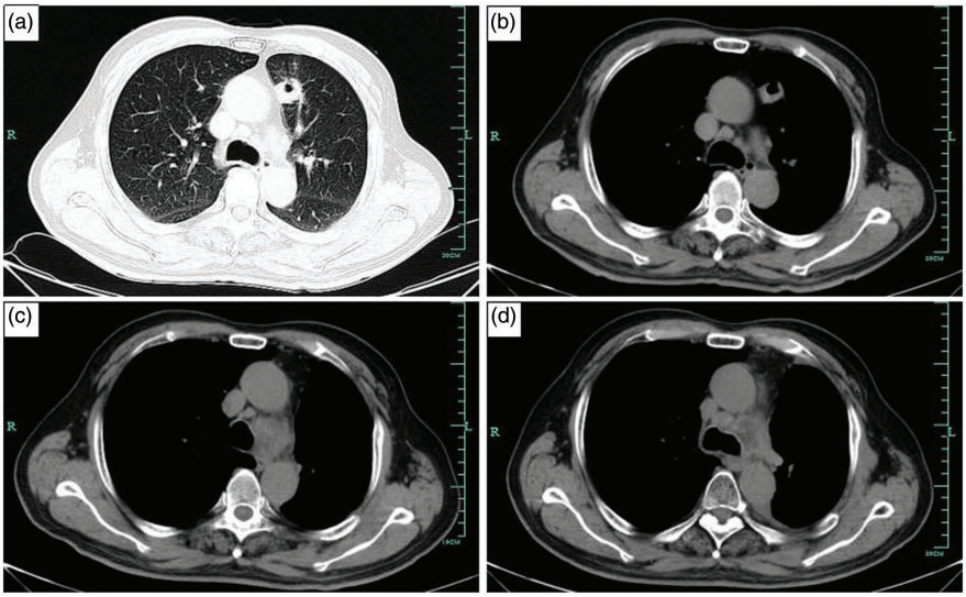

Figure 1. Computed tomography images. (a, b) A 25-mm-diameter mass with a cavity was found in the left upper lung lobe. (c) Six months after surgery, a large lymph node was found in the mediastinum. (d) The lymph node in the mediastinum was smaller after radiochemotherapy.

nuclei that varied in size and shape. Epidermoid differentiation was observed, and mucus-secreting glandular cells and intermediate cells were confirmed by hematoxylin–eosin staining (Figure 2(a), (b)). Immunohistochemically, the tumor was positive for tumor protein 63 (Figure 2 (c)), epidermal growth factor receptor (EGFR) (Figure 2(d)), Ki-67 protein, cytokeratin 7, and cytokeratin 5/6. It was negative for thyroid transcription factor 1, vimentin, synaptophysin, chromogranin A, neural cell adhesion molecule (CD 56), and napsin A. Although EGFR was overexpressed, the EGFR mutational status was negative by the high-sensitivity polymerase chain reaction method. Hematoxylin–eosin and special staining of the tumor led to a diagnosis of high-grade MEC. According to the lung cancer TNM staging system (Union for International Cancer Control, 2009), the pathological stage was IA: T1bN0M0 (the mass size was $25 \times 23 \times 20$ mm). The tumor had invaded the upper lobe bronchial cartilage, but not more proximal than the lobar bronchus. All resection margins were negative for tumor involvement, and the lymph nodes of groups 4, 5, 7, 10, 11, 12, 13, and 14 were free of metastatic disease.

Six months after surgery, the patient developed a hoarse voice. Chest CT showed a large lymph node in the mediastinum (Figure 1(c)), and lymphatic metastasis was considered. The patient was treated with radiochemotherapy consisting of radiotherapy (60 Gy in 30 fractions) and chemotherapy (cisplatin at 40 mg/m^2 on days 1, 7, 14, 21, 28, 35, and 42). The treatment led to a partial response in that the lymph node in the mediastinum decreased in size (Figure 1(d)).

Ten months after surgery, the patient presented again with cough, dyspnea, and hemoptysis. Eleven months after surgery, he developed a headache. We repeated the

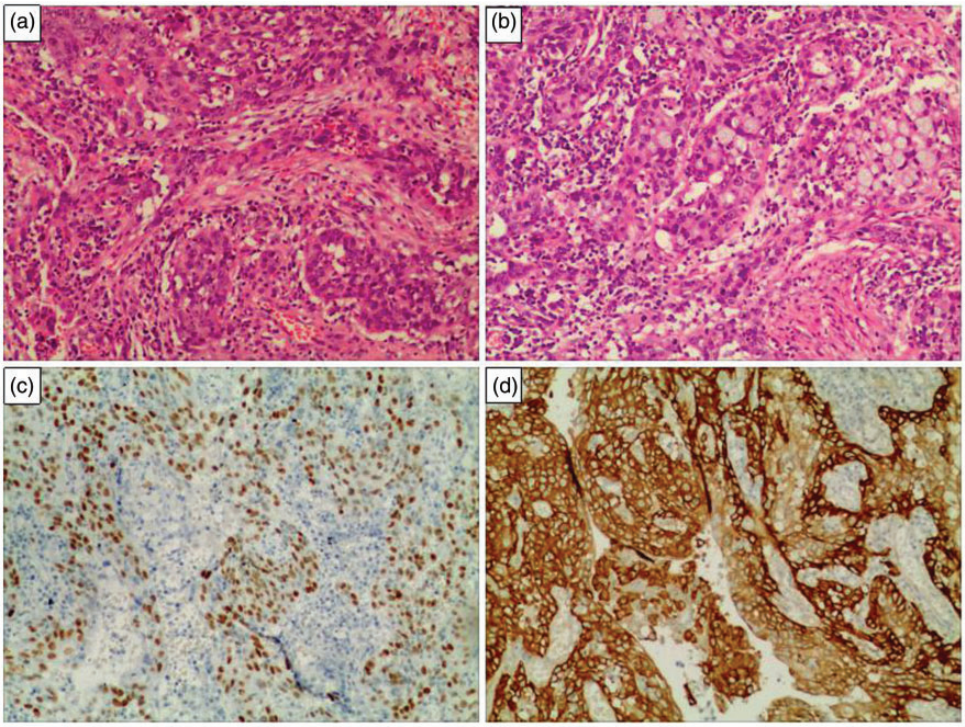

Figure 2. Histopathologic images. The tumor was composed of epithelioid cells distributed in nests (**a**: hematoxylin and eosin staining; magnification, 100×) with a mixture of mucus-secreting glandular cells and intermediate cells (**b**: hematoxylin and eosin staining; magnification, 100×). Immunohistochemically, the tumor was positive for tumor protein 63 (**c**: EnVision method; magnification, 100×) and epidermal growth factor receptor (**d**: EnVision method; magnification, 100×).

whole-body emission CT examination, which showed abnormal enhancement of the metabolism of the skull, right eighth rib, L5 vertebra, and left femur. The patient was considered to have widespread metastasis. Head magnetic resonance imaging revealed no signs of intracranial metastasis. Chest CT showed pericardial and pleural effusion. Lymphadenectasis of the left neck was also present; the largest node was 1.0 cm in diameter. Twelve months after surgery, the patient did not require any adjuvant therapy and died of respiratory failure.

Discussion

Pulmonary MEC is a rare malignant neoplasm that mostly affects younger age groups. MEC is classified into low-grade and high-grade MEC based on its histological features, and little is known about its prognostic factors. High-grade MEC is a more aggressive form of malignancy than low-grade MEC. Few cases of primary pulmonary MEC with a cystic airspace, especially high-grade pulmonary MEC, have been reported worldwide. The World Health Organization classifies pulmonary MEC as a "salivary gland type" tumor, along with pulmonary adenoid cystic carcinoma and epimyoepithelial lung carcinoma.[5] Most reports of MEC involve young persons. Additionally, although pulmonary MEC occasionally presents as a peripheral mass, it more often presents as a mass in the trachea, the carina, or a mainstem bronchi.

MEC appears to have no association with smoking or other risk factors for bronchial carcinoma, such as asbestos exposure.[6] Our patient was an advanced-age smoker with a peripheral lung mass and presented with the common clinical symptoms and signs of MEC, including cough, dyspnea, and hemoptysis.[7]

The mechanism underlying the formation of cystic lung cancer progresses as follows.[8] First, inflammation or tumor formation causes bronchial obstruction and stenosis, leading to lung space expansion. Second, the central part of the tumor becomes necrotic, and the liquid necrotic substance is discharged through the bronchus, forming a lucid area. Third, the tumor grows along the wall of the previously existing bulla, or the wall of the lung around the cavity thins secondary to elastic retraction. Farooqi et al.[9] and Yamada et al.[10] conducted in-depth and detailed comparative CT and pathologic studies, confirming the presence of infiltration and spread of lung cancer cells on the cystic wall. Therefore, we have good reason to suspect that exfoliation of tumor cells on the cystic wall is responsible for the development of early metastasis.

Histologically, MEC is classified into low- and high-grade types. Low-grade tumors rarely metastasize and have a good outcome, but high-grade tumors are aggressive and tend to exhibit early metastasis and local invasion.[11] In a series of 18 pulmonary MECs, all 3 high-grade tumors were fatal within 16 months, whereas 12 patients who underwent resection of low-grade tumors were alive at the last follow-up (the mean follow-up period was 4.7 years).[12] In the present case, the patient was found to have lymphatic metastasis 6 months after surgery and survived for only 12 months after surgery.

Surgical resection is the primary treatment method for MEC, especially for patients with early-stage disease. In patients with unresectable, incompletely resectable, or enhanced tumors, adjuvant radiotherapy is necessary, but adjuvant chemotherapy is not. There is no clear evidence of the benefit of chemotherapy for pulmonary MEC. Only a few case reports have described chemotherapy for pulmonary MEC. In one study, 3 of 14 patients with MEC showed partial responses to treatment with paclitaxel (200 mg/m^2 every 21 days).[13] Another case report indicated that treatment with carboplatin and paclitaxel was effective in 2 of 14 patients with recurrent salivary gland carcinoma.[14] The patient in the present case was treated with radiochemotherapy based on the above reports. No guidelines indicate the necessity of radiotherapy or chemotherapy for stage IA pulmonary MEC; thus, we performed neither radiotherapy nor chemotherapy because of the lack of supporting data until lymph node metastasis was found. We chose cisplatin for chemotherapy with radiotherapy because cisplatin is in the same classification as carboplatin and has a radiosensitizing effect. However, the patient did not have a good response to the radiochemotherapy.

According to some case reports, EGFR is frequently overexpressed in MEC, but few cases are positive for EGFR mutations. Tyrosine kinase inhibitor (TKI) therapy has been reported to achieve a partial response in both cases with and without EGFR mutations.[15,16] The role of TKI therapy in metastatic MEC is unclear, especially in patients who show a response to TKI therapy but in whom no activating EGFR mutations are detected in the tumors. The tumor in the present case showed EGFR overexpression by immunohistochemistry, but the tumor was negative for EGFR mutation. TKI therapy was not performed because of its high cost.

Conclusion

This report has described a rare case of a primary pulmonary high-grade MEC with a

cystic airspace in a 77-year-old man who underwent successful surgical resection but subsequently developed rapid metastasis and a poor outcome because of the tumor's aggressive behavior, even in the early stage. We hypothesized that the early metastasis in this case was caused by seeding of tumor cells through the cystic airspace, although there is no definitive evidence for this phenomenon. This case and other reports suggest that adjuvant treatment is necessary for primary pulmonary high-grade MEC at any stage. Radiochemotherapy can be a treatment option, although it achieves only a partial response. The outcome in this case might have been different if the radiochemotherapy had been performed earlier. Further studies are needed to determine whether the presence of a cystic airspace has an effect on metastasis and whether early adjuvant therapy is needed.

Acknowledgment

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Ethics

The publication of this case report and all accompanying images was approved by the Ethics Committee for Clinical Research of Lishui Municipal Center Hospital. Written informed consent was obtained from the patient's family for the publication of this case report.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Availability of data and materials

The data supporting the conclusions of this article are included within the article.

Authors' contributions

CY, ZFB, and YLP drafted the manuscript. ZXY, ZCH, ZFB, CY, and CXM performed the surgery. CY, YLP, and CXM collected and analyzed the clinical and physiological data. ZCH performed critical revisions for important intellectual content. ZCH, YLP, and ZFB edited the manuscript. CY, ZFB, CXM, YLP, ZXY, and ZCH reviewed the manuscript. All authors read and approved the final manuscript.

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