Unusual pulmonary nodules diffusion from epithelial-myoepithelial carcinoma on ^{18}F-FDG PET/CT: A case report

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Abstract. Epithelial-myoepithelial carcinoma (EMC) is a rare low-grade malignant tumor with uncommon regional lymph node metastasis and distant metastasis. The diagnosis of this disease primarily relies on the examination of pathological morphology and immunohistochemical staining, as its clinical symptoms and imaging findings are non-specific. This makes it more difficult to provide specific information about EMC lung metastasis. The present report describes a biopsy-confirmed case of pulmonary metastases arising from EMC of the parotid. The pulmonary nodules were dispersed throughout both lungs and exhibited varying degrees of fluorodeoxyglucose (FDG) uptake on positron emission tomography-computed tomography scans. Additionally, the pathological and immunohistological presentation of the lung mass was similar to that of the primary lesion. Several pulmonary nodules exhibiting varying degrees of FDG uptake may be considered a distinctive sign of metastasis on EMC imaging. Reviewing the present case, along with other similar rare cases in the literature, is crucial to accurately evaluate the imaging examinations of such patients to identify and establish an appropriate treatment plan for potential metastatic lung cancer. It also highlights the importance of not underestimating the malignant potential of EMC and the necessity for close follow-up.

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Abbreviations: EMC, epithelial-myoepithelial carcinoma; FDG, fluorodeoxyglucose; CT, computed tomography; PET/CT, positron emission tomography-CT; MRI, magnetic resonance imaging; CK, creatine kinase

Key words: EMC, metastatic lung cancer, PET/CT, ^{18}F-FDG, immunohistochemistry

Introduction

Epithelial-myoepithelial carcinoma (EMC), previously known as malignant myoepithelial tumor and myoepithelial carcinoma, was first reported in 1972 by Donath *et al* (1). In 1992, the World Health Organization classified it as a separate salivary gland tumor (2). EMC is a rare, low-grade malignant salivary gland-type tumor arising in the head and neck region, occurring in ~1% of salivary gland adenomas and ~2% of all malignant tumors of the salivary gland (3). The parotid gland is the most common site of EMC, followed by the submandibular gland and minor salivary glands, and occasionally the lacrimal gland (4), maxillary sinus (5), nasopharynx (6), pituitary gland (7), tongue (8), trachea (9), esophagus (10), lungs (11) and mammary glands (12). Despite its propensity for local recurrence and low metastatic potential, it rarely exhibits invasive behavior in remote tissues and organs (13). A positive surgical margin is associated with an increased risk of recurrence, whereas adjuvant radiotherapy was associated with a reduced risk of local disease recurrence. The optimal management strategy for EMC remains undetermined. In addition to complete surgical treatment, postoperative radiation or chemotherapy is administered depending on the patient condition (5). Most of the relevant literature records to date, especially for distant organ metastasis of EMC, are case reports, which generally lack more detailed imaging data and morphological feature descriptions. In the present report, the relevant data of a case of lung metastasis from parotid epithelial-muscle epithelial carcinoma were collected, its imaging manifestations and pathological features were analyzed in detail, and the relevant literature was reviewed, to deepen the understanding of the disease, highlight the malignant potential of the disease and provide a reference for its clinical diagnosis.

Case report

A 60-year-old man presented to Binzhou Medical University Hospital (Binzhou, China) in December 2017 with a left retroauricular swelling for >1 month, accompanied by tinnitus and numbness on the left side of the face after cold stimulation

for the previous 10 days. On physical examination, a painless, poorly mobile mass measuring 3x3x2 cm was detected deep to the lower border of the mandible. Initial ultrasound imaging revealed that the mass was a solid, space-occupying lesion occurring in the parotid gland (data not shown). In January 2018, computed tomography (CT) of the parotid gland further confirmed that there was a space-involving lesion in the parotid region (Fig. 1A). Additionally, enhanced dual-source spiral CT of the oropharynx revealed the presence of foci of abnormal enhancement within the parotid gland, thereby suggesting a heightened probability of the lesion being malignant. The patient denied any previous history of hypertension, infectious diseases, hereditary familial disorders or smoking. Consequently, in January 2018, the patient underwent a left parotidectomy, lumpectomy and cervical lymphatic dissection. Intraoperatively, it was observed that certain branches of the facial nerve were adherent to the tumor in the deep lobe, necessitating the careful performance of facial nerve anastomosis. Postoperative pathological observation revealed a greyish-yellow solid texture of the tumor section and no metastasis in the cervical lymph nodes. Immunohistochemistry demonstrated positivity for P63, pan-cytokeratin (CK), CK7, CD117, S-100 and P63. The final diagnosis was left parotid EMC and the patient was discharged after receiving one course of local radiotherapy.

In January 2023, the patient returned to the hospital reporting chest tightness and hemoptysis. Initial abdominal ultrasound revealed no significant abnormal lesions; however, axial chest CT indicated the presence of multiple randomly distributed nodules in both lungs, suggesting the possibility of lung metastasis (Fig. 1B). Routine blood, liver biochemistry, stool and urine testing, as well as examination of tumor markers such as carcinoembryonic antigen, non-small cell lung cancer antigen, neurogen-specific enolase and squamous cell carcinoma-associated antigen showed no significant abnormalities. The patient underwent ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT and fine-needle aspiration biopsy (Fig. 1C) for further diagnosis. The maximal intensity projection revealed numerous FDG-avid lesions in the chest (Fig. 2A). The PET and PET/CT fusion images demonstrated varying degrees of FDG uptake among these nodules (Fig. 2C and F). While certain nodules exhibited markedly elevated FDG uptake [maximum standardized uptake value (SUV_{max}), 8.8; Fig. 2B and D], others displayed lower (SUV_{max}, 3.3) or negligible (SUV_{max}, 1.0; Fig. 2E and G) FDG uptake. Additionally, lymph nodes with increased FDG uptake were observed in the hila and mediastinum. Pathological analysis of the puncture tissues from the pulmonary nodules confirmed the presence of epithelial-myoepithelial cells (Fig. 3A). Immunohistochemical staining showed columnar cells inside the glandular ducts were CK+, EMA+, CD117+, CK7+ (Fig. 3B), and the clear cells outside the glandular ducts were P63+ (Fig. 3C), S-100+ (Fig. 3D), and the Ki-67 positive rate was about 10%. The pathological diagnosis was EMC. Based on an extensive evaluation considering the medical history of the patient, a conclusive diagnosis of pulmonary metastatic EMC was made. The case timeline is presented in Fig. 4. After the diagnosis of lung metastases from EMC, an expert opinion from a radiation oncologist was obtained, and the patient was advised to undergo postoperative radiation therapy. Treatment was refused by the patient and family and therefore, a regular strict follow-up (including regular physical and CT examinations) was planned. A total of 6 years after left parotidectomy and 20 months after confirmation of lung metastases, without the use of any drugs or treatment, the patient had not experienced any local recurrence or abnormally enlarged lung nodules.

Staining methods. For staining, the tissue was fixed with 4% neutral formalin for 24 h, embedded in paraffin, and made into 3 μm continuous sections, which were placed in an oven at 60˚C for 60 min. HE staining was performed using a standardized program stainer (Tissue-TekFilm-JC2) for 70 min and observed using an OLYMPUS optical microscope (OLYMPUS BX53-DP22). For immunohistochemical staining, 4 μm sections were used for staining. The procedures were all performed using the BOND-MAX issued by Leica and the Benchmark Ultra fully automatic immunohistochemical stainer issued by Roche. The immunohistochemical experimental procedures were standardized for staining. The primary and secondary antibodies were antibodies produced by Fuzhou Maixin Biotechnology Co., Ltd. and Beijing Zhongshan Jinqiao Biotechnology Co., Ltd. The sections were observed using an OLYMPUS optical microscope (OLYMPUS BX53-DP22).

Literature review

The PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science databases (https://www.webofscience.com/wos/woscc/basic-search; as of August 1, 2024) were searched for case reports and case series of EMC with lung metastasis. Adults with relevant imaging information were considered first. Inclusion criteria were case report studies on EMC with lung metastasis (e.g., epithelial-myoepithelial carcinoma and lung metastasis) written in English and published after 1990, with a description of pulmonary metastatic nodules in the literature. Exclusion criteria comprised studies published before 1990 and those penned in languages other than English. For each relevant case report, the first author, publication year and country, as well as the sex, age, primary tumor location, time of lung metastases detection, CT and PET-CT imaging findings, methods of diagnosis, treatment and follow-up results of the patient were recorded (Table I).

A systematic database search revealed that nine studies (14-22) reported EMC with lung metastases prior to the case reported in the present study. Of these, 5 patients were male and 4 were female. There was no regional bias in the occurrence of EMC diseases. Most of the lesions occurred in the parotid gland. Most lung metastases from EMC appeared as multiple nodules in both lungs on chest X-ray or CT. However, PET-CT was performed in only three studies, and two of them characterized the FDG uptake of the nodules. As in the present case, one study demonstrated mild to moderate FDG uptake. A total of 6 patients in these studies received radiation or chemotherapy, and only 1 had a good prognosis so far.

Discussion

EMC is a rare low-grade malignancy in which >70% of patients are >60 years of age, evenly distributed in sex, or have a slight female predominance (23). Different from the clinical presentation of common salivary gland malignancies (faster growth,

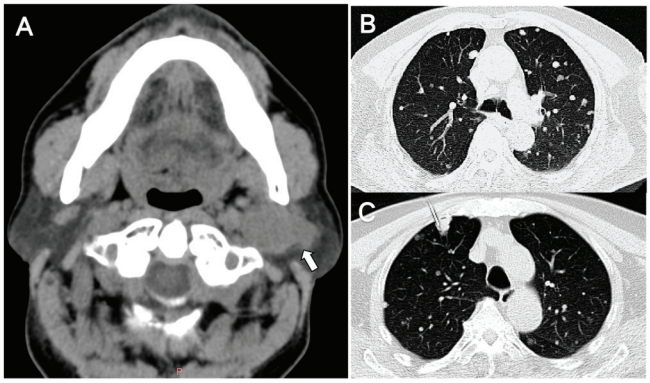

Figure 1. CT findings of epithelial-myoepithelial carcinoma in the parotid gland and pulmonary metastasis.. (A) CT of the parotid gland indicated the presence of a space-occupying lesion in the parotid region. (B) Axial chest CT reveals the presence of multiple randomly distributed nodules in both lungs. (C) Precise fine-needle aspiration biopsy completed under positron emission tomography-CT guidance. CT, computed tomography.

more painful symptoms and invasion of nerves), this tumor usually presents as a slow-growing asymptomatic mass (23).

Despite being a low-grade malignancy, EMC has a tendency to recur locally and can invade adjacent nerves, blood vessels and bones. However, regional lymph node metastasis and distant metastasis are uncommon, occurring in <5% of cases (13). Luna *et al* (24) reviewed the data of 9 cases of EMC, of which 5 had tumor recurrence and 1 had metastases to the cervical lymph nodes and lungs. A case of a patient with epithelial-muscle epithelial cell carcinoma of the parotid gland who developed lung metastases and two local recurrences 14 years after the initial resection has also been reported in the literature (22). In a review of 58 patients with EMCs, only 3 patients (5.2%) showed signs of metastatic disease, with just 1 case exhibiting distant metastasis to the iliac bone (25). In the largest review of 246 cases of EMCs, 11 patients (4.47%) had distant metastases; however, the specific locations were not mentioned (26). In the present case, lung metastasis occurred 5 years after parotid EMC, indicating that the aggressive nature of EMC should not be underestimated and warrants careful examination in clinical practice. Furthermore, it has been reported that tumor necrosis is associated with distant metastasis and poor clinical prognosis (27,28). Seethala *et al* (25) reported that positive margins, vascular lymphatic infiltration, tumor necrosis and myoepithelial abnormalities, including severe nuclear atypia or pleomorphism, were notably associated with tumor recurrence. As a result, close monitoring is crucial, particularly if the tumor shows signs of necrosis and exhibits aggressive characteristics upon pathological examination.

The diagnosis of EMC relies on pathologic patterns, as well as immunohistochemical staining. Gross pathology reveals a multinodular white mass, the majority of which are well-defined and often lack or only partially have an enclosing membrane (29). Infiltrative growth patterns are observed in only ~12% of cases, and identifying tumor infiltration visually is challenging. Most sections exhibit a solid, gray or grayish-yellow appearance along with hemorrhage and necrosis, whereas a few have cystic areas with internal papillary projections. Most of these cystic or necrotic areas may arise from high-grade cancerous areas or from poorly differentiated or undifferentiated areas, and as a result, exhibit the presence of inactive nodules on PET-CT radiographic images (SUV for tumor activity) (3). In the present case, the tumor microscopically showed a mixture of lobulated, tubular and solid nests or sheets. The typical histopathology of EMC involves a biphasic tubular structure, consisting of inner layer lined with eosinophilic ductal epithelial cells and an outer layer of hyaline myoepithelial cells. The cytoplasm of clear muscle epithelial cells contains glycogen (30). Cellular uptake of ^{18}F-FDG is proportional to the rate of glycogen metabolism. In most cases, tumor cells do not exhibit malignant characteristics. However, recurrences, particularly those with a predominance of hyaline cells, display distinct anisotropy, karyorrhexis and necrosis, occurring in ~18% of cases. This structure demonstrates infiltrative growth, and the ratio between the two cell types can vary (3). Additionally, a network of different histological subtypes may be present, contributing to the difficulty in diagnosing EMC due to its histological diversity, complexity and heterogeneity (3). These microscopic manifestations can be reflected by the differing metabolic rates of each nodule on PET-CT (31), as observed in the present case, but are not feasible with conventional examinations. PET-CT is useful in determining the activity of tissue metabolism (32). Analyzing the characteristics of tumor biological behavior, we hypothesize that the unusual presentation of lung metastatic nodules may be related to the presence of varying degrees of necrosis or histological complexity within the tumor. A previous study also reported that the histologic grading of EMC appeared to be associated with the level of FDG uptake (33). Immunohistochemistry reveals varying degrees of positivity for specific markers of epithelial cells such as CK, CK7 and epithelial cell membrane antigen in most EMCs. Specific markers such as S-100, smooth muscle actin, P63 and Calponin are also positively expressed to varying degrees in tumor cells (34). If the characteristic double-layered tubular structure is seen in the biopsy specimen, combined with immunohistochemical dual expression of the epithelial myoepithelial component, this can lead to a definitive diagnosis. In the present case, a double-layered tubular structure was observed in the lung biopsy tissue, and immunohistochemistry also confirmed the presence of CK7, p63 and S-100 with varying degrees of positive expression. The morphological spectrum of EMCs is broad, with multiple histologic subtypes and variants, and metastatic sites may show multiple growth patterns (25). Therefore, in addition to incorporating a significant medical history at the time of diagnosis, it is crucial to be able to incorporate PET-CT manifestations that reflect the atypical spread patterns of these nodules.

Increased availability of imaging modalities such as ultrasound, CT and MRI has improved the diagnostic sensitivity for epithelial-muscle-epithelial (EME) cancers presenting as neck masses. It can also increase the detection of EME cancers that are incidentally found using diagnostic imaging for unrelated reasons (35). In a case of left parotid EMC (36), MRI revealed a well-defined lobulated mass with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Suto *et al* (29) summarized the cases of 7 patients with EMC of the parotid gland and found that although the MRI features of EMC were similar to those of benign salivary gland tumors or low-grade malignant salivary adenocarcinomas, a multinodular structure and internal septa were characteristic of EMC after cross-referencing with histological findings. There

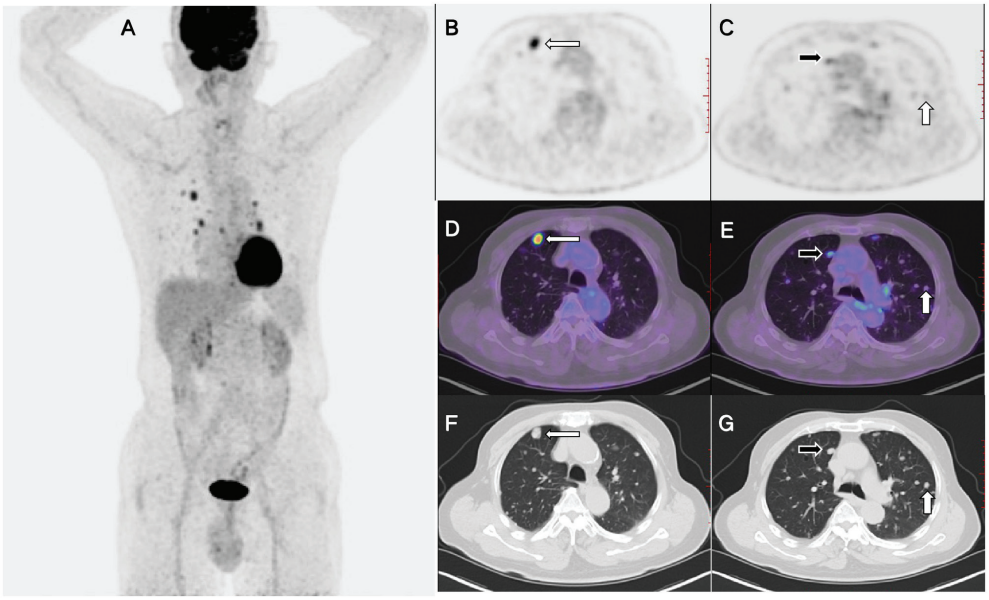

Figure 2. PET/CTfindings of pulmonary metastasis from EMC. (A) Maximal intensity projection reveals a numerous number of lesions with FDG uptake in the chest. (B) EMC lung metastases exhibit high FDG uptake on PET. (C) EMC lung metastases exhibit low or neglibible FDG uptake on PET. (D) PET/CT fusion images showed high FDG uptake. (E) PET/CT fusion images showed low or neglibible FDG uptake. (F) Appearance of nodules with high FDG uptake on CT image. (G) Appearance of nodules with low or neglibible FDG uptake on CT image.FDG, fluorodeoxyglucose; CT, computed tomography; PET, positron emission tomography; EMC, epithelial-myoepithelial carcinoma.

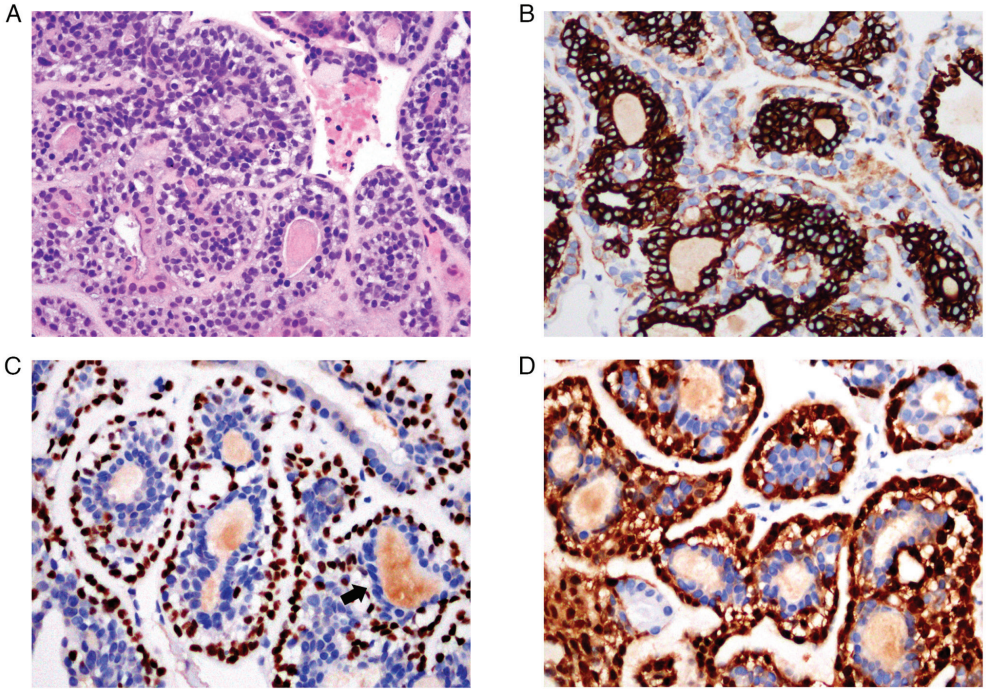

Figure 3. Typical histopathology of epithelial-myoepithelial carcinoma consisting of an inner layer lined with eosinophilic ductal epithelial cells and an outer layer of clear myoepithelial cells. (A) This biphasic tubular structure can be clearly observed in the lung tissue using hematoxylin and eosin staining (magnification, x400). Immunohistochemical analyses were positive for (B) CK7 (magnification, x400), (C) p63 (magnification, x400) and (D) S-100 (magnification, x400).

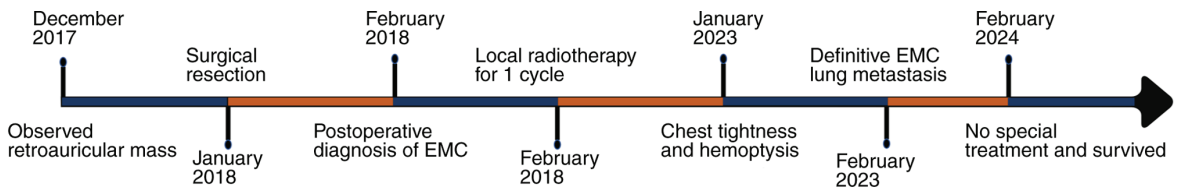

Figure 4. Timeline of EMC progression in the present case. EMC, epithelial-myoepithelial carcinoma.

Table I. Clinical and imaging features of the cases of epithelial-myoepithelial carcinoma with lung metastases based on the literature review.

First author/s, year	Country	Sex	Age, years	Primary EMC location	Time of metastases	Chest X-ray/CT	PET-CT	Methods of diagnosis	Treatment	Follow up	(Refs.)
Civan *et al*, 2024	Turkey	F	51	Parotid gland	5 years after surgery	Multiple nodular lesions in both lungs	Mild to moderate FDG uptake	Biopsy	Chemotherapy	NA	(14)
Mäkelä *et al*, 2020	Finland	F	36	Salivary gland	4 years after surgery	Multiple small nodules in right lung	NA	Biopsy	Chemotherapy and targeted medical therapy	Died ~11 months later	(15)
Chen *et al*, 2017	Australia	M	52	Base of tongue	Found along with the primary lesion	NA	Bilateral multiple pulmonary nodules. No significant FDG uptake	NA	Palliative care	Died after 18 months	(16)
Hsieh *et al*, 2016	Taiwan	M	43	Right parotid gland	3 years prior to the primary lesion	A total of three nodular lesions in left lung	NA	Postoperative pathology	Thoracoscopic surgery	NA	(17)
Yamazaki *et al*, 2013	Japan	M	35	Right parotid gland	10 months after surgery	Small nodular lesions in both lungs	NA	Progression lesions	Adjuvant radiotherapy	No recurrence or metastasis in 2 years	(18)
Yang *et al*, 2012	China	F	60	Left submandibular gland	15 months after surgery	Multiple nodular lesions in both lungs	NA	NA	NA	Lost to follow-up	(19)
Pierard *et al*, 2006	Belgium	M	51	Submandibular gland	3 years after surgery	Multiple parenchymal nodules in both lungs	Bilateral multiple pulmonary nodules	Biopsy	Chemoradiotherapy	Died after 30 months	(20)
Kasper *et al*, 1999	Germany	F	58	Left parotid gland	12 years after surgery	Multiple nodular lesions in right lung	NA	Biopsy of the mass lesion	Palliative chemotherapy	Dies after 3 years	(21)
Noel *et al*, 1992	USA	M	63	Left parotid gland	14 years after surgery	Multiple pulmonary nodules in both lungs	NA	Biopsy	NA	Minimal tumor growth 5 months later	(22)

M, male; F, female; EMC, epithelial-myoepithelial carcinoma; CT, computed tomography; PET, positron emission tomography; NA, not applicable; FDG, fluorodeoxyglucose.

have also been case reports of PET/CT scans revealed high 18F-FDG affinity at the EMC primary site (37) or peripheral regions exhibiting an irregular ring of strong FDG uptake with a lack of central photons (38). Due to the low rate of distant organ metastasis in EMC, imaging manifestations associated with metastasis are less commonly reported. In patients with lung metastasis, chest CT often shows a well-defined rounded mass with multiple satellite nodules extending from the lung lobes to the left lower lobe (22) or scattered multiple nodules (39). Histologically, the lung tumor is similar to a previously detected parotid tumor that could serve as an important diagnostic basis. However, there are few reports on the PET/CT imaging manifestations of consistent with the observations in the present case. Only one recent case report demonstrated multiple lung lesions with mild to moderate FDG uptake similar to the present case (14). In comparison with the present case, the number of lesions reported in the literature is relatively smaller, with larger nodule sizes and similar degrees of FDG uptake. Notably, the present case presents with small and numerous EMC lung metastasis nodules with varying FDG uptake. However, nodules with high SUV values should be monitored in subsequent follow-up. PET/CT is not only quantitative but can also provide valuable information about the pathophysiology of tumors, receptor expression, metabolism or morphological and functional characteristics, such as oxygenation or tissue density, and pharmacodynamic properties of drugs (40). In recent years, the use of more specific imaging agents for PET/CT has not only opened up novel avenues for tumor imaging, but has also brought the integration of diagnosis and therapy to a novel stage of development. Due to the recent advancements in imaging techniques, this presentation of atypical findings on PET-CT has a significant value in differential diagnosis and follow-up of disease recurrence.

Due to the low prevalence of EMC, there are fewer treatment experiences to draw on and the relevant studies lack big data support (3). Most reports emphasize its diagnosis and pathology, with fewer research advances involving its treatment. Surgery is the preferred treatment option and thoroughness is essential. As the rate of hematogenous metastasis of EMC is not low, it is crucial to perform liver CT, lung CT, bone scans or whole-body PET-CT examinations to detect any potential distant metastases. Postoperative chemotherapy may be beneficial in combating hematogenous metastasis. Additionally, head and neck EMC is often associated with HRAS mutations (30.0-82.7%) and the mutation sites are mostly concentrated in codon 61 of exon 3 (HRAS Q61R) (41). Consequently, HRAS codon 61 mutations could serve as important molecular markers for EMC. Therefore, intensive clinical, imaging, pathologic and molecular examinations are necessary to assess EMC risk stratification and management.

In conclusion, the present report describes a rare case of EMC with pulmonary metastases that exhibited distinctive imaging manifestations. Diffusely distributed lung nodules that exhibit varying degrees of FDG uptake can be considered as unique characteristics resembling metastasis on EMC imaging. Furthermore, the present report emphasizes that the malignant potential of EMC cannot be underestimated. Careful physical examination, meticulous pathologic and molecular observation, comprehensive treatment and frequent imaging follow-ups are important factors in tightly monitoring disease recurrence and metastasis.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YCW, NJG, YNZ, WBX and HSS contributed to the study conception and design. NJG, YNZ and WBX analyzed data. YCW and HSS wrote the manuscript. YCW, NJG, YNZ, WBX and HSS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures in the present study were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration.

Patient consent for publication

Written informed consent was obtained from the patient for publication of the present case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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