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A Case Report of Multiple Lymph Node Metastatic Adenocarcinoma Without Primary Lesion (Probable Source of Salivary Glands)

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1. Abstract

1.1. Rationale: Salivary gland cancer is a rare malignant tumor of the head and neck. We provide a rare case, a malignant and poorly differentiated adenocarcinoma with no clear primary lesion and multiple regional lymph node metastasis. In terms of treatment, chemotherapy, targeted therapy and immunotherapy were explored and positive effects were achieved.

1.2. Patient concerns: A 48-year-old female who has been present with upper abdominal pain for more than 2 years. Imaging studies revealed multiple regional lymph node enlargement. There were no abnormal masses or nodules in other organs.

1.3. Diagnoses: The patient was clinically diagnosed as an aggressive, poorly differentiated adenocarcinoma with multiple lymph node metastases. Histologically, the lymph node tissue has ductal and myoepithelial (strongly calponin-positive, focal smooth muscle actin-positive) components and a prominent biphasic proliferation of epithelial structure. The pathological diagnosis was epithelial-myoepithelial carcinoma. Whole exome sequencing was identified as FGFR amplification.

1.4. Interventions: The patient received cisplatin in combination with fluorouracil chemotherapy for 2 cycles, docetaxel in combination with amlotinib for 4 cycles and maintenance therapy with amlotinib for 10 months, finally received programmed cell death protein 1 (PD-1) for 3 cycles.

1.5. Outcomes: The patient was followed up 14 months after amlotinib therapy without disease progress. This patient got extensive progressive disease and death occurred 32 months after initial treatment.

1.6. Lessons: Whole exome sequencing may provide an effective treatment for rare metastatic tumors with unknown primary lesion.

2. Introduction

Salivary gland cancer is a histologically diverse head and neck malignancy, accounting for about 3%-5% of all head and neck cancers. It has a variety of biological behaviors, and its incidence is rising slowly worldwide. Donath et al. first discovered a low-grade malignant tumor differentiated from epithelial and myoepithelial cells in salivary glands in 1972, which was named epithelial myoepithelial carcinoma [1]. EMC (epithelial-myoepithelial carcinoma) is a rare tumor that occurs mainly in the parotid gland, with an incidence of less than 1% in salivary gland cancer. It is a low-grade malignant tumor with local infiltration and growth and easy recurrence. The neck lymph node metastasis rate is 10%~20%, and distant metastasis is rare [2,3]. Diagnosis is mainly done by histopathology andimmunohistochemistry. Here, we present a case of a malignant, poorly differentiated adenocarcinoma with multiple regional lymph node metastases. Clinical or radiological evidence

does not indicate a clear primary lesion, butpathological diagnosis suggests ductal myoepithelial components and a biphasic structure, which was inclined to be EMC.

3. Case report

A 48-year-old female patient complaining of upper abdominal discomfort for more than 2 months. The patient had no history of smoking and her past medical history was unremarkable. The physical examination revealed an swollen lymph node in the left neck, measuring 2.5×1.5cm, distinct borders. PET-CT(positron emission tomography computed tomography) suggesting multiple enlarged lymph nodes in the left supraclavicular / subclavian region, mediastinum, right hilum of lung, right diaphragmatic foot, hepatogastric space, and retroperitoneal region, with abnormal increase in metabolism. The clinical stage was TxN3M1, stage IV. Biopsy pathology of left supraclavicular lymph node showed metastatic adenocarcinoma. Microscopically, the tumor cells showed Homogenous group piece, relatively consistent, transparent cytoplasm, moderate atypia, and lumen in some areas. On immunohistochemical examination, the tumor cell was positive for Calponin, CK8/18, E-cadherin, Villin , S-100 and negative for LCA, Syn, CD56, CK20,PAX8, TTF-1,P63,P40, GATA-3, CK5/6, Calretinin, SMMHC, PCK (strongly cavity surface epithelial-positive, weakly myoepithelial-positive), EMA (cavity surface epithelial-positive, myoepithelial-negative), SMA (focal smooth muscle actin-positive), focal CgA-positive, β-catenin (membrane positive), CK7 (partial-positive), CDX2 (focal-positive), WT1 (partial cytoplasmic-positive). The ki-67 index was 10% (Figure 1).

Since the early symptoms of myoepithelial carcinoma are not obvious, lacking characteristic clinical manifestations, imaging examination can only provide information such as lesion scope and infiltration degree, so definite diagnosis mainly depends on histopathology and immunohistochemical examination. EMC is a biphasic tumour, comprising a regular repetitive mixture of two cells type. The main histological features of EMC are epithelial cells in the inner layer of the lumen and myoepithelial cells surrounding the outer layer [4,5]. A traditional marker of myoepithelial cells is SMA, a good indicator of their smooth muscle characteristics. Other myoepithelial markers, such as S100, calponin and CK14 have been used. The inner luminal epithelial cells are negative for SMA and positive with cytokeratin markers, e.g. AE1/AE3, CAM5.2 and pancytokeratin (PCK) [6].

In our case, immunohistochemical examination excluded lymphoma (LCA, CD56 negative) and squamous-cell carcinoma, supported adenocarcinoma (CK8/18 positive). The outer myoepithelial cells tested positive for SMA and Calponin, while the inner epithelial cells were positive for pancytokeratin(PCK). Therefore, the pathological diagnosis was inclined to EMC.

In the period of June 19, 2018 and July 20, 2018, the patient received two courses of chemotherapy comprising 5-fluorouracil (5-FU) plus cisplatin(5-FU 750mg:day1-4, and cisplatin 30mg:-day1-4, every 21 days). Contrast-enhanced computed tomography (CT) scan suggested multiple nodules in both lungs were metastases. Efficacy was evaluated as progress. The whole exome sequencing showed FGFR amplification (Table 1), which is in line with the target drug target of anlotinib. In the period of August 17, 2018 and November 15, docetaxel in combination with anlotinib (docetaxel 55mg:day1\day4, anlotinib 12mg:day1-14, every 21 days)was taken for 4 cycles. CT showed that the lymph nodes were slightly smaller and some larger than the anterior lymph nodes. Pulmonary nodules were stable (Figure 2). The efficacy was evaluated as stable. After that, the patient receive danlotinib(12mg:day1-14, every 21 days) in maintenance therapy. The patient had stable disease for 10 months. On October 25,2019, CT scan revealed the range of lymph nodes and multiple nodules in both lungs were larger than before. During October 29, 2019 to December 2, 2019, Pd-1 200mg was taken for 3 cycles. However, lymph nodes enlarged significantly were observed on the CT scan with progress disease. The patient died 32 months after the initial treatment.

Table 1: Whole exome sequencing of patient: Tumor key driver gene list

Mutant gene	Signal path/molecular mechanism	Mutant site/mutant status	frequency/copy number
FGFR1	FGFR	Amplification	3.3
Tumor mutation load	New antigen formation	High	-
MYC	MYC	Amplification	3.91
ATR	DNA reparation	P.L69F	57.14%

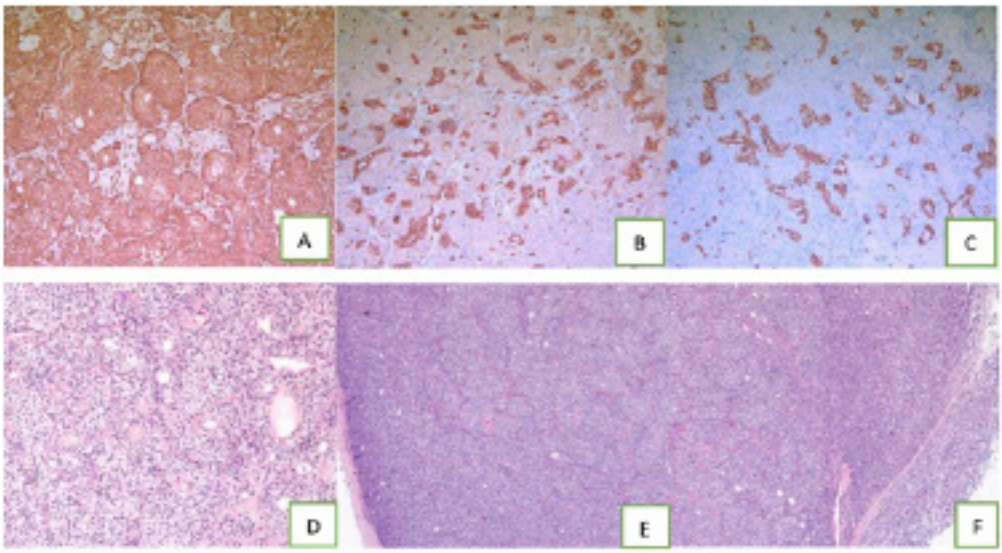

Figure 1: Immunohistochemical staining of section (original magnification × 100). A , The outer-layer cells are positive for Calponin as myoepithelial marker. B, C, The inner-layer cells are positive for epithelial markers pan-cytokeration and epithelial membrane antigen, respectively.Hematoxylin-eosin–stained section (original magnification, × 40). D, E, F, the cells show Homogenous group piece, relatively consistent, transparent cytoplasm, moderate atypia, and lumen in some areas.

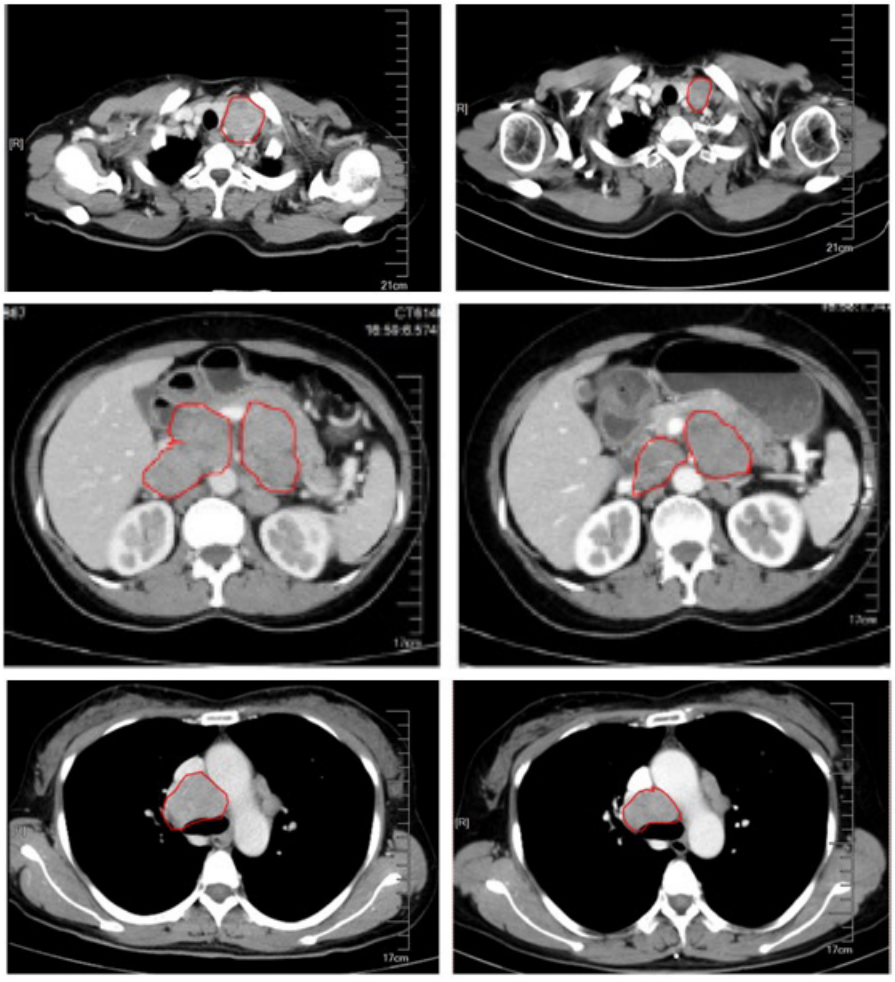

Figure 2: The enhanced CT comparison between the first admission(2018.06.17) and after 6 cycles of treatment with anlotinib (2019.05.31). The lymph nodes are significantly narrowed.

4. Discussion

Based on the morphological characteristics of the cells in our case, the main differential diagnosis to be considered was pulmonary epithelial-myoepithelial carcinoma. Pulmonary epithelial-myoepithelial Carcinoma are very rare. Because of their origin from the tracheobronchial submucosal glands, pulmonary Epithelial-Myoepithelial Carcinoma are often central lesions that present as endobronchial tumor masses [7-12]. As a result, patients commonly present with signs and symptoms of bronchial obstruction, including shortness of breath, cough, hemopt-ysis, chest pain, fever, or pneumonia [13]. More rarely, peripheral parenchymal tumors may occur, the majority of which are asymptomatic and detected incidentally [14-16]. In this case, abdominal discomfort was the only symptom and the imaging findings were lymph node enlargement. There was no evidence of bronchial or vascular infiltration. It is remarkable the negative of epithelial cells for TTF-1, which suggest that the tumour not has a pneumocytic differentiation [16]. Pulmonary epithelial-myoepithelial carcinoma was excluded in this case.

Due to the extremely low incidence rate of EMC, there are few treatment experiences to be used for reference, and the relevant studies lack of the support of bulk data. Most case reports are emphasis on diagnosis and pathology of EMC, less for treatment. For primary salivary adenocarcinoma without distant metastasis, surgical resection and local radiotherapy are preferred [17]. Palliative treatment is usually selected to salivary adenocarcinoma, which cannot be treated with operation or radiotherapy and has local recurrence and distant metastasis. Palliative treatment usually chooses chemotherapy [18]. Conventional chemotherapy drugs for salivary adenocarcinoma were cisplatin and azithromycin [19]. The most widely used drugs are cisplatin combined with anthracycline [20]. At present, systematic chemotherapy for epithelial - myoepithelial carcinoma of salivary glands is rarely reported. There has been a case report in which lung metastases of primary EMC of the parotid gland treated with docetaxel, cisplatin and fluorouracil chemotherapy, followed 9 months later, which evaluated as CR [21]. Pierard S et.al shows a case report in which lung metastases of primary EMC of the submandibular gland were treated with regimen of cisplatin plus fluorouracil and paclitaxel plus cyclophosphamide separately, which got a stable disease to a certain extent [22].

Studies have found that epidermal growth factor receptor (EGFR) is overexpressed in head and neck cancer, which is associated with the activation of EGFR-dependent signaling pathway and leading to the disease of tumor cell proliferation and anti-apoptotic recurrence [23]. FGER mutations most frequently occur in the tissues of polymorphous adenocarcinoma (20%), pleomorphic adenocarcinoma carcinoma (9%) and mucoepidermoid carcinoma (7%). Myoepithelial carcinoma and EMC are associated with FGFR-PLAG1 or PLAG1-TGFRβ [24]. By treating two patients with metastatic salivary gland carcinoma treated with docetaxel in combination with trastuzumab and pastuzumab, Wim et al. found that dual HER2 blocking and multi-line HER2 targeted therapy were beneficial for her2-positive patients with metastatic salivary gland carcinoma [25].

In this case, the whole exome sequencing of the patient indicated FGER gene amplification, and the test report indicated that the best matching targeted drug for the patient was anrotinib. As a novel small-molecule multi-target tyrosine kinase inhibitor (TKI), anlotinib has a strong inhibitory effect on the target of VEGFR, PDGFR, FGFR and c-kit, and also has effects of anti-angiogenesis and anti-tumor growth [26]. Therefore, anlotinib can inhibit tumor growth and delay the progression of the disease by interfering with FGFR expression. The patient treated with anlotinib maintain stable disease for 14 months.

Our study has certain limitations, in terms of pathological diagnosis, because of the salivary gland carcinoma showing a heterogeneity of histological manifestations and the particularity of this case which has no primary lesions clearly, pathologic diagnosis only tends to be sources of salivary gland. The perspective of clinical diagnosis provides the basis for the possible source of metastatic adenocarcinoma and makes the diagnosis more inclined.

5. Conclusion

The systematic and standard chemotherapy guidelines for salivary epithelial myoepithelial carcinoma are still not known, and it is a clinical blind spot. In this case, antinib had good effective of treatment. we expect that our case report would provide a method to the treatment of this rare cancer in the future. As for this kind of rare tumor, we can take the whole exome sequencing to find the corresponding drug target then select the appropriate target drugs, and antiangiogenic drugs may be tried for treatment. In this case, the immunotherapy did not show a good therapeutic effect. In the future, we will increase the sample size to clarify the efficacy of immunotherapy for EMA and the screening of specific groups, so as to provide evidence for the effective treatment of EMA.

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