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Case Report

Palatine tonsillar metastasis of lung adenocarcinoma: an unusual immunohistochemical phenotype and a potential diagnostic pitfall

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Abstract: Metastasis rarely occurs to the palatine tonsils. Herein, we present an exceedingly rare case of palatine tonsillar metastasis from poorly differentiated lung adenocarcinoma with anaplastic lymphoma kinase (ALK) mutation in a 51-year-old woman. The patient manifested clinically as pharyngalgia without obvious respiratory symptoms, with swelling tonsil histomorphologically resembling lymphoma and partially expressing the markers of epithelial and squamous cell carcinoma (CK5/6, P63, and P40). Due to the non-specific immunohistochemical expression, it is easily misdiagnosed as a primary poorly differentiated squamous cell carcinoma of the tonsil. This case highlights the importance of a comprehensive assessment of suspicious tonsillar lesions, that may be a sign of a primary malignancy elsewhere in the body.

Keywords: Lung adenocarcinoma, metastasis, tonsil, anaplastic lymphoma kinase (ALK)

Case description

A 51-year-old female with symptoms of discomfort and pain in her throat for the duration of 20 days, treated in our department, was examined to disclose a mass with ulcers and necrosis in the left palatine tonsillar fossa. A tissue biopsy showed atypical neoplastic cells that were diffuse and densely distributed (**Figure 1A**). The cells were medium in size, single, and adherent to each other. The nucleus was round and medium-sized, with prominent nucleoli which were located in the center of the nucleus. Most cells were in mitosis, and no necrosis was observed in these cells. Immunohistochemical stains showed the neoplastic cells in the palatine tonsil were positive for EMA, CD10 and pan-CK (**Figure 1C**), partially positive for p63, p40 and CK5/6 (**Figure 1D**), strongly positive for ALK P80 (**Figure 1E**), but negative for other B cell lymphoma correlation markers (CD20, CD3, CD4, CD8, CD5, CD30, PAX5, BCL2, BCL6, MUM1, C-MYC), malignant melanoma (S-100, HMB45) and follicular dendritic cell sarcoma (CD21, CD35). Synthesizing the characteristics of the partial expression of squamous epithelial carcinoma markers p63, p40 and CK5/6 by neoplastic cells and the high proliferation ki-67 rate, the patient was diagnosed as poorly-differentiated squamous cell carcinoma and geared up for tonsillectomy and cervical lymphadenectomy. In view of the strongly positive expression of ALK P80, we further ordered the pulmonary computed tomography (CT) examination. Enhanced CT scan revealed that a soft tissue mass in the lower lobe of the left lung was observed, the bronchi were truncated, the lesion's border was less clearly surrounded by visible burrs, lower left lobe was slightly smaller, and CT value was enhanced by enhancement scanning. There were enlarged pulmonary hilum, neck and mediastinal lymph nodes, and a small arc liquid density shadow could be seen in the left chest. A positron emission tomogra-

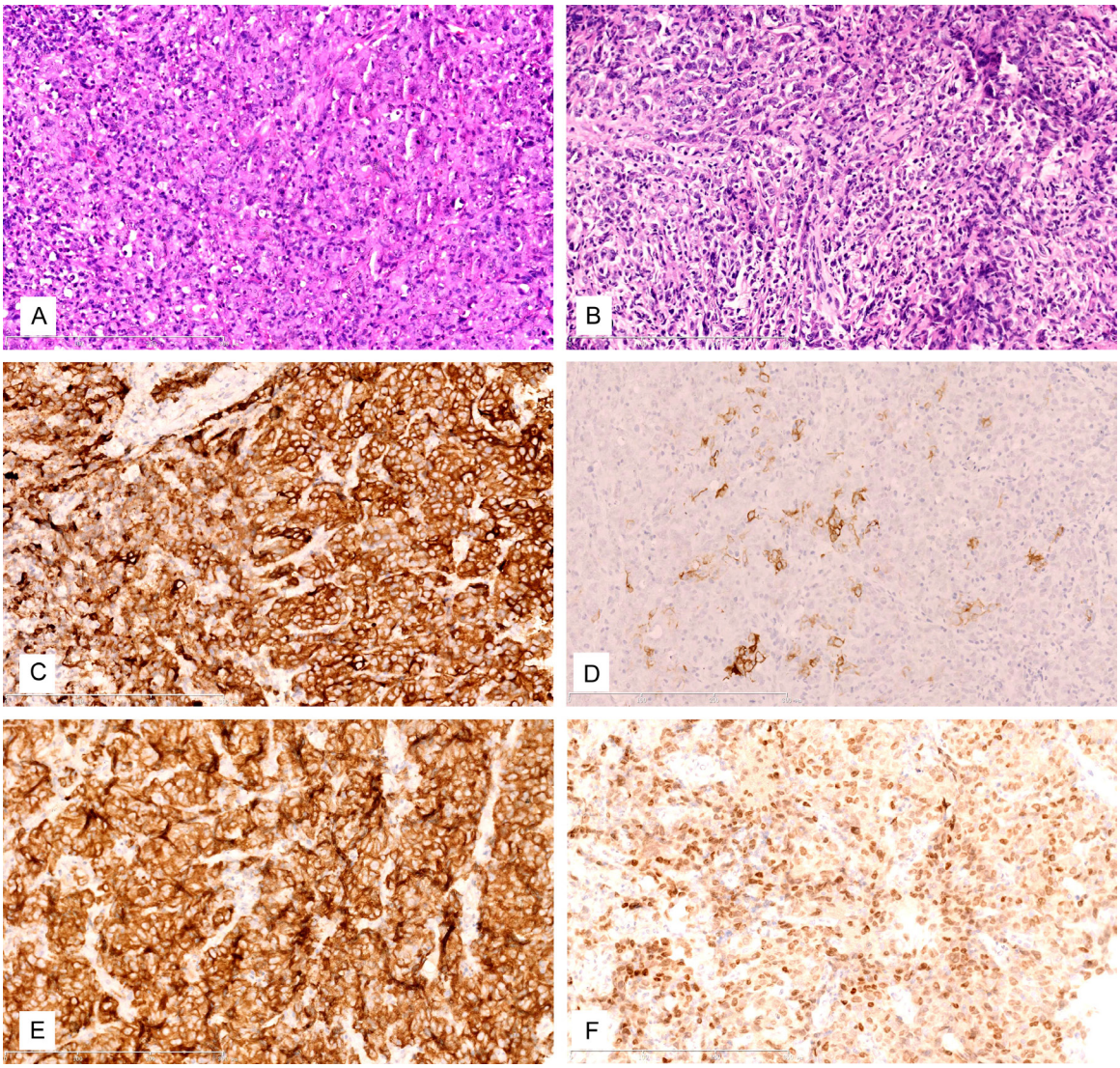

Figure 1. A. The tonsil neoplastic cells had diffuse distribution with abundant cytoplasm and prominent nucleoli (Original magnification ×200, scale bar 300 μm). B. The histologic morphology of lung tumor tissue was similar to that of tonsil. (Original magnification ×200, scale bar 300 μm). C. Immunohistochemical results showed that tonsil neoplastic cells were positive for broad spectrum CK (Original magnification ×200, scale bar 300 μm). D. Few tonsil neoplastic cells were positive for CK5/6 (Original magnification ×200, scale bar 300 μm). E. ALK P80 was strongly positive in tonsil neoplastic cells (Original magnification ×200, scale bar 300 μm). F. TTF-1 was diffusely positive in tonsil neoplastic cells (Original magnification ×200, scale bar 300 μm).

phy/computed tomography (PET/CT) scan detected abnormal cell metabolism, indicating primary tumor metastasized to the colon, liver, spleen and right lobe of thyroid. We also observed enlarged lymph nodes with increased cell metabolism in the left neck, double supraclavicular, mediastinum, double pulmonary hilum, and hepatic hilum. Thus, malignant lesion metastasis was considered. Subsequently, the patient underwent an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) showing histologic morphology similar to that of the tonsil (**Figure 1B**). As TTF1 was positive in lung which always indicates a poorly differentiated adenocarcinoma, we further performed the TTF1 immunohistochemistry of the tonsil tumor, and the result was diffusely positive too which gave a sign of metastasis of lung cancer (**Figure 1F**). ARMS PCR was performed to detect EGFR, ALK and ROS1 genomic alteration profiles in lung cancer tissues. Interestingly, the ALK fusion gene

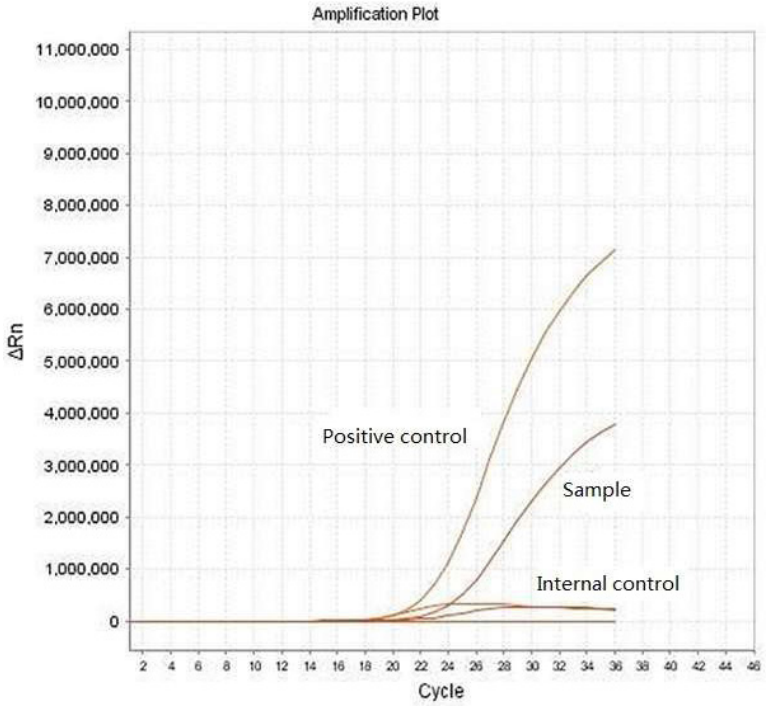

Figure 2. ARMS PCR showed ALK mutation in lung cancer tissue.

mutation was positive (**Figure 2**), while EGFR and ROS1 gene analysis revealed no mutations.

The patient was eventually diagnosed with a poorly differentiated adenocarcinoma of the lower lobe of the left lung with left tonsil and multiple organ metastases (T2N3M1, stageIV). She was transferred to the department of oncology and prescribed crizotinib for targeted anti-tumor treatment, followed up closely. Unfortunately, the patient died of disseminated disease 5 months later after two cycles of chemotherapy.

Discussion

Lung adenocarcinoma metastasizing to the tonsil is an extremely rare malignancy with a poor prognosis, and may be a pitfall for clinicians [1]. Although the pathway by which malignancies metastasize to the tonsil remains controversial and difficult to determine, hematogenous spread, retrograde cervical lymphatic spread through the thoracic duct, or implantation metastasis during bronchoscopy [2] may be the potential mechanism. A metastatic tumor in an unusual site may make it troublesome to distinguish between a synchronous or metachronous primary cancer and a metastatic disease, especially when it is asymptomatic. In general, primary tonsil tumors are mostly squamous cell carcinoma and lymphoma; other pathological types are rare. In the present case, the histomorphology changes of tonsil resembled lymphoma, while the histologic manifestations of palatine tonsil tumor cells showed a squamous epithelial phenotype that was positive for pan-CK, EMA, P63, P40 and CK5/6. It is easily misdiagnosed as a primary poorly differentiated squamous cell carcinoma of the tonsil. Highly variable results have been reported over the years, particularly for the prevalence of 'squamous markers' in adenocarcinoma [3-6]. As a single marker, only diffuse TTF-1 was specific for adenocarcinoma whereas none of the 'squamous markers', even if diffuse, were entirely specific for squamous cell carcinoma. Therefore, a combination of multiple immunohistochemical markers is helpful for the correct diagnosis of some atypical cases.

In addition, we noticed ALK P80 protein was positive immunohistochemically in our case. We also found EML4-ALK fusion gene mutation in lung adenocarcinoma. ALK oncogenic properties were initially identified in anaplastic large cell lymphoma (ALCL) accompanied by a unique reciprocal chromosomal translocation t (2;5) (p23;q35) in 1994 [7, 8]. This rearrangement yields a fusion gene called NPM-ALK thus resulting in the expression of an 80-kD oncogenic fusion protein designated ALK P80. Afterward, ALK was discovered to be rearranged, mutated, or amplified in such a series of tumors as diffuse large B-cell lymphoma (DLBCL) [9], inflammatory myofibroblastic tumor (IMT) [10] and other diseases [11-16]. There is strong preclinical evidence that ALK may be a driving force of oncogenesis in these cases. Lung adenocarcinoma is a kind of malignant tumor with high heterogeneity in both histology and molecular genetics. As in our case, protein expression of ALK P80 was positive in EML4-ALK fusion lung adenocarcinoma. Although the predominant translocations such as NPM-ALK in ALCL and

EML4-ALK in NSCLC are very characteristic for their respective tumor types, some ALK fusion proteins are occasionally shared by these histologically diverse tumors. Currently, there is no research on whether there are oncogenes in the metastasis of lung cancer to the tonsils, and the correlation of tumorigenesis, metastasis, and poor survival rate in ALK fusion gene and fusion protein is not clear, but deserves further study.

As an important therapeutic target discovered in the field of lung cancer, ALK gene analysis should be routinely conducted at the same time as diagnosis for advanced NSCLC, adenocarcinoma, or other types of lung cancer with adenocarcinoma components. Patients with EML4-ALK fusion gene mutation generally have distinct clinical and pathological characteristics, such as relatively young age of diagnosis (about 50 years old), no gender preference, non-smoking or light smoking, and are prone to early lymph node metastasis. Most of them are adenocarcinoma abundant in signet ring cells [17]. Both symptom remission rate and median progression-free survival can be significantly improved after ALK-TKI inhibitor administration [18]. In our case, the patient received crizotinib as targeted anti-tumor therapy. The initial effect was dramatic with lung tumor shrinkage. Unfortunately later she died of drug resistance, multiple metastases, and systemic diseases.

Metastatic palatine tonsil cancer from a primary lung adenocarcinoma is an extremely rare malignancy with a poor prognosis. Metastasis in the palatine tonsil as the first symptom and having no obvious respiratory symptoms may be a pitfall for clinicians, and hence the advanced clinical stage of the disease is often found when first diagnosed. Comprehensive physical, immunohistochemical, and genetic examination can determine the source and nature of tumors, provide strong evidence for accurate diagnosis, treatment, and improvement of prognosis. Individualized treatment strategies can be formulated according to patients' pathologic types, molecular genetic characteristics, and physical states to maximize the survival time, control the disease progression and improve the quality of patients' life.

Disclosure of conflict of interest

None.

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