Clinical Case Report

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A case report of tongue metastasis from lung squamous cell carcinoma and literature review

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Abstract

Rationale: Tongue metastasis from lung cancer is extremely rare, and the prognosis of these patients is rather poor.

Patient concers: A 56-year-old man was found a 4-cm cavity lesion in the left upper lobe, which was initially misdiagnosed as tuberculosis.

Diagnoses: A case of lung squamous cell carcinoma that metastasized to the base of a patient's tongue.

Intervations: We send the biopsy of the lung and the tongue lesions for gene sequencing.

Outcomes: He received systemic chemotherapy, but continued to have pain at the base of his tongue and died 7 months later.

Lessons: From sequencing data, mutations in KRAS proto-oncogene, GTPase (KRAS), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and tumor protein p53 (TP53) were found in the tumor biopsy of the patient. All of these were indicators of poor prognosis.

Abbreviations: ALK = anaplastic lymphoma kinase, CDKN2A = cyclin-dependent kinase inhibitor 2A, CT = computed tomography, CTCF = CCCTC-binding factor, EGFR = epidermal growth factor receptor, KRAS = KRAS proto-oncogene, GTPase, MRI = magnetic resonance imaging, NCOR1 = nuclear receptor corepressor 1, NSCLC = non-small-cell lung cancer, PET-CT = positron emission computed tomography, PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, PPD = purified protein derivative, SCC = small-cell cancer, TBX3 = T-box 3, TKIs = tyrosine kinase inhibitors, TP53 = tumor protein p53.

Keywords: gene mutation, literature review, lung squamous cell carcinoma, poor prognose, tongue metastasis

1. Introduction

Lung cancer, of which 80% to 85% is non-small-cell lung cancer (NSCLC), is the leading cause of cancer-related mortality around the world.[1] Distant metastasis from primary lung cancer—e.g., to brain, liver, adrenals, or bone—is quite common; however, metastases to the tongue are relatively rare.[2] In a previous report, primary lung cancer metastasized to the tongue was found in 1.6% of 3047 cases.[3] About 5% of all malignant lesions were found in the oral cavity,[4] and 1% of them were from primary sites other than the oral cavity.[5] As tongue is a rare metastatic site, when a lesion is detected, a thorough evaluation to distinguish between metastasis or primary cancer should be made.[6] As lingual metastases tend to occur mostly in patients who have general dissemination of primary malignancies,[3] their prognoses tend to be poor.

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XC and ZH contributed equally to this work.

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This study was approved by Committee on Ethics of Biomedicine, Second Military Medical University. This patient has given the informed consent of the study.

2. Case report

A 56-year-old male electric welder with an ongoing 30-pack-year smoking history was referred to the People's Hospital of Yancheng, Jiangsu province, with a complaint of cough with intermittent bloody sputum for 1 month and a half, without fever breathlessness or chest pain. No abnormalities were found in physical examination of his respiratory system. The thoracic computed tomography (CT) showed a 4-cm cavity lesion in the left upper lobe and multiple mediastinal lymphadenopathy. It was initially misdiagnosed as tuberculosis; subsequently, he accepted irregular antituberculosis treatment.

However, a week later, this patient became aware of a lump on the base of his tongue and experienced pain and hoarseness. He was therefore admitted to the Department of Respiratory Medicine, Changhai Hospital. Physical examination showed stiffness on the base of the tongue, but no ulcerated lump. Thoracic CT results were similar to b (Fig. 1A and B). However, neck magnetic resonance imaging (MRI) showed a 3.6-cm infiltrating mass arising from the base of the tongue and multiple cervical lymphadenopathies (Fig. 1C and D). The laryngoscope showed lymphoid tissue hyperplasia on the base of the tongue and the left vocal cords were fixed (Fig. 2A and B). CT-guided biopsy of lung lesion yields the diagnosis of squamous cell carcinoma (SCC; Fig. 3A and B). A biopsy of the tongue lump also showed squamous tumor cells (Fig. 3D), similar in appearance to the biopsy of lung. Based on these findings, the tongue lesion was diagnosed as a metastatic tumor from the lung cancer. A positron emission computed tomography (PET-CT)

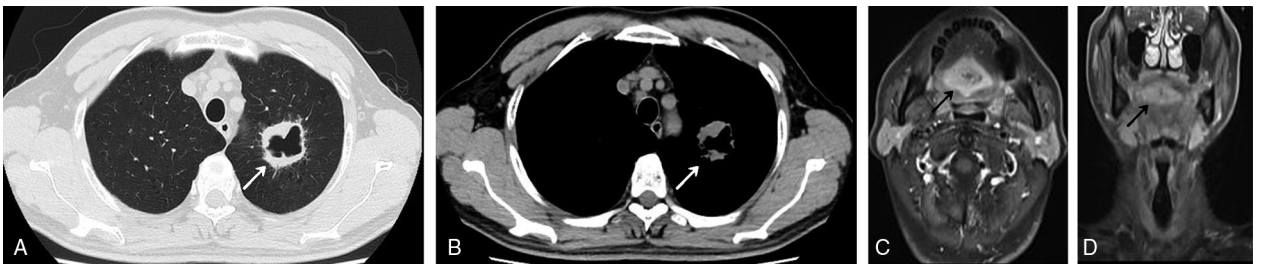

Figure 1. Chest CT and neck MRI. A, B, The CT scan shows a 4-cm cavity lesion in the left upper lobe and multiple mediastinal lymphadenopathy. C, D, The neck MRI shows a 3.6-cm infiltrating mass arising from the base of the tongue and multiple small cervical lymphadenopathies. CT = computed tomography, MRI = magnetic resonance imaging.

showed no metastasis to bone, liver, or brain. The patient was diagnosed as T4N0M1b, stage IV left upper lobe lung SCC with metastases to the base of the tongue, according to the TNM staging system.[7] Subsequently, he received platinum-based doublet chemotherapy (Table 1). The DC regimen, which consists of docetaxel (100 mg, d1) and carboplatin (400 mg, d1), repeated every 21 days, was given as first-line treatment on July, 2016. After 2 courses of chemotherapy, the patient underwent CT scan, which revealed a progress of the disease, and he continued to have pain at the base of his tongue. Instead of continuing with the other combination chemotherapy, the patient received a paclitaxel/Nida's platinum regimen (paclitaxel: 210 mg on day 1; Nida's platinum: 400 mg on days 1–4; repeated every 21 days) from September 2016 to the time of he died (February 16, 2017).

3. Genomic analysis

3.1. High-throughput sequencing

Targeted sequencing of the lung cancer tissue was performed at Berry Genomics Co, Ltd (Beijing, China). Targeted sequences were enriched using Integrated DNA Technologies xGen Pan-Cancer Panel v1.5 (Coral, IL). A genomic DNA library was prepared using the Nextera DNA Library Prep Kit (Illumina, San Diego, CA), and was quantified by Eco Real-Time PCR System (Illumina, San Diego, CA). The quantified library was sequenced on the Illumina (San Diego, CA) HiSeq 2500 platform with 2 × 150 bp configuration.

The average sequencing depth of targeted regions is ×520.9. For bases in targeted regions, 99.92% are covered at least once, and 99.34% have over ×50 read depth.

3.2. Data processing

Adaptor sequences and bases with low qualities were trimmed off from the raw reads during preprocessing and quality control by using Flexbar (version 2.4). The reads were then aligned to the hg19 (GRCh37) version of human genome using Burrows-Wheeler Aligner, version 0.7.5. The resulted alignments were sorted by SAMtools (version 0.1.19), and after which the PCR duplications were marked using Picard tools (version 1.57). To further increase specific mutation calling, we used Genome Analysis tool kit (version 3.3-0) for realignment and base recalibration. Somatic single nucleotide substitutions were called by combined using of VarScan2 (version 2.3.7) and MuTect (version 1.1.7), and somatic small indels were detected by combined use of SomaticIndelDetector (GATK version 2.3.9) and VarScan2 (version 2.3.7).

Fisher exact test was performed on every locus in which a second allele was detected, to improve the sensitivity of mutation calling. The functional regions and the effects of resulting mutations were annotated by Annovar (ver. 2016Feb01).

4. Discussion

Primary lung cancer usually presents as an airway mucous membrane irritation, such as cough and blood-stained sputum,

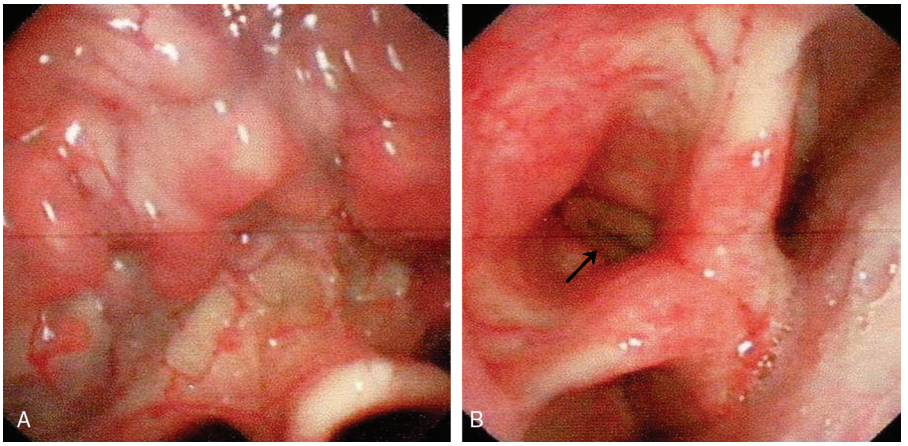

Figure 2. The laryngoscope shows (A) lymphoid tissue hyperplasia at the base of the tongue, and (B) fixed left vocal cords.

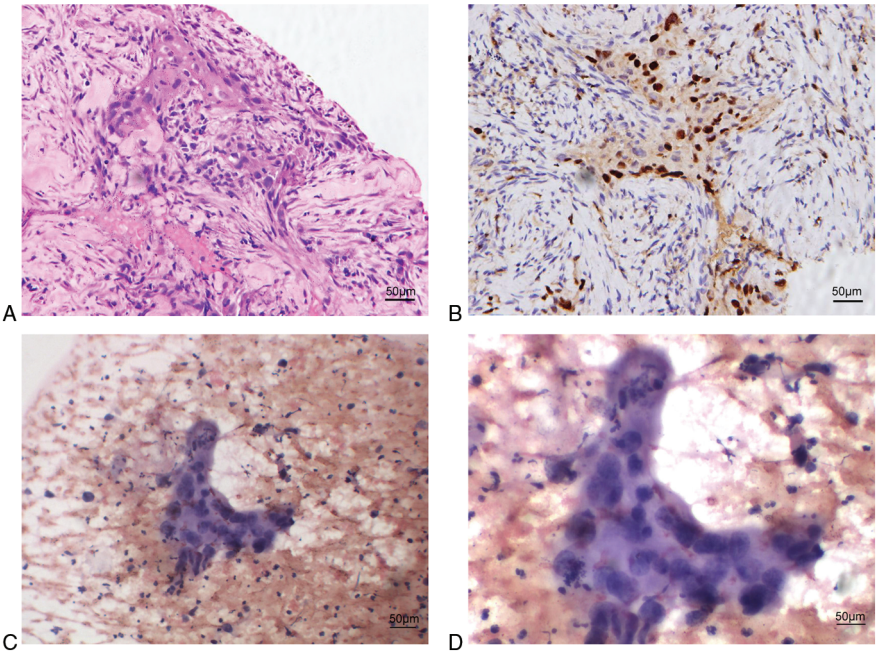

Figure 3. A, B, CT-guided biopsy of lung lesion yielded the diagnosis of squamous cell carcinoma (papanicolaon stain ×100), tumor cells displayed polygonal, cubic, abundant amounts of eosinophilic cytoplasm, nucleus was oval, arranged in a cord-like and invasive growth. C, D, The tongue biopsy showed a squamous cell carcinoma whose appearance was similar to that of the lung (C, papanicolaon stain ×200; D, papanicolaon stain ×400). CT = computed tomography.

whereas primary tongue carcinoma usually presents with tongue lesions, pain, and dysphagia.[8] This patient initially presented with a cough with intermittent bloody sputum and subsequently became aware of a lump on the base of his tongue and experienced pain and hoarseness. According to these clinical characteristics, medical images, and pathological examinations, we diagnosed the tongue lesion as a metastatic tumor from the lung cancer.

Indeed, it is difficult to identify tumors or tuberculosis in a lung cavity lesion. In general, tuberculosis is usually manifested as low fever, night sweats, fatigue, weight loss and other symptoms and blood antituberculosis antibody detection or purified protein derivative (PPD) skin test could be positive. It was too hasty to diagnose this patient as tuberculosis initially without the typical clinical manifestations of tuberculosis and positive laboratory findings.

Reported incidence of metastases from NSCLC to the tongue varies between 0.2% and 1.6%.[6] Primary NSCLC spreads to distant organs by 3 routes: systemic, venous, or lymphatic circulation.[2] Lingual metastases occur mostly in patients whose primary lung cancers are generally disseminated; their prognoses tend to be rather poor (Table 2). This patient's rare tongue metastasis likely occurred through lymphatic circulation rather than systemic or venous dissemination, as his PET-CT showed there was no widespread metastasis to other sites. As with primary tumors of the tongue, metastatic lesions to the tongue may be ulcerated or polypoid.[6] Tongue metastasis can also cause pain, bleeding, discomfort, difficulty in swallowing, or dyspnea. Although rare, tongue metastasis should be considered under these circumstances, especially in cases with nonulcerated masses on the base of the tongue; appropriate investigation should be undertaken.[3]

Platinum-based doublet chemotherapy has been a standard treatment for patients with advanced stage NSCLC for many years.[9] Improved understanding of the biology of NSCLC has led to a dramatic change in the therapeutic landscape of this disease. Treatment of selected patients with advanced NSCLC that harbors specific oncogenic alterations, including epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements, had been revolutionized.[10,11] Biomarker-driven therapies, such as those for EGFR and ALK, and tyrosine kinase inhibitors (TKIs) such as gefitinib,

Table 1

Combination therapeutic regimens and treatment results.

	Regiments	Number of courses	Treatment results
DC	Docetaxel (100 mg, d1) Carboplatin (400 mg, d1)	1	Progressive disease July 13, 2016–August 6, 2016
Docetaxel + cisplatin	Docetaxel (100 mg, d1) Cisplatin (400 mg, d1–4) Paclitaxel (210 mg, d1)	1	Progressive disease August 6, 2016–September 20, 2016
Paclitaxel+ Nida platinum	Nida platinum (400 mg, d1–4)	3	Progressive disease September 20, 2016–February 16, 2017

Table 2

Studies of lung cancer with tongue metastasis.

Author, reference	Basic information	Pathology	Metastatic sites	Multimodality therapy	Survival months
Jeba et al[2]	45-yr-old male smoker	Adenocarcinoma	Tongue, lung, liver, adrenals, kidneys, pancreas, duodenum, intra-abdominal lymph nodes	Carboplatin/pemetrexed chemotherapy	Lost to follow-up
Terashima et al[3]	63-yr-old male smoker	Squamous	Tongue, lung, liver, adrenal gland, pericardium, heart, subcutaneous tissues	Radiation to lingual lesion, brain, muscular metastases; docetaxel/carboplatin chemotherapy	5 mo
Mui et al[4]	65-yr-old male smoker	Large cell	Tongue, bone	Radiation to lingual lesion, neck and lung; cisplatin chemotherapy	4 mo
Kurt et al[6]	57-yr-old male smoker	Squamous	Tongue, parenchymal nodules, T12 vertebral	Cisplatin, docetaxel/cisplatin, gemcitabine chemotherapy	Lost to follow-up
Tsubochi et al[16]	39-yr-old male Nonsmoker	Adenocarcinoma	Lingual tonsillar, jugular, lymphade-nopathy	Surgery to lung cancer; radiation to lingual tonsillar	8 yr
Xiangwen et al[22]	39-yr-old female Nonsmokers	Squamous	Tongue, brain, bone	Chemotherapy	3 mo

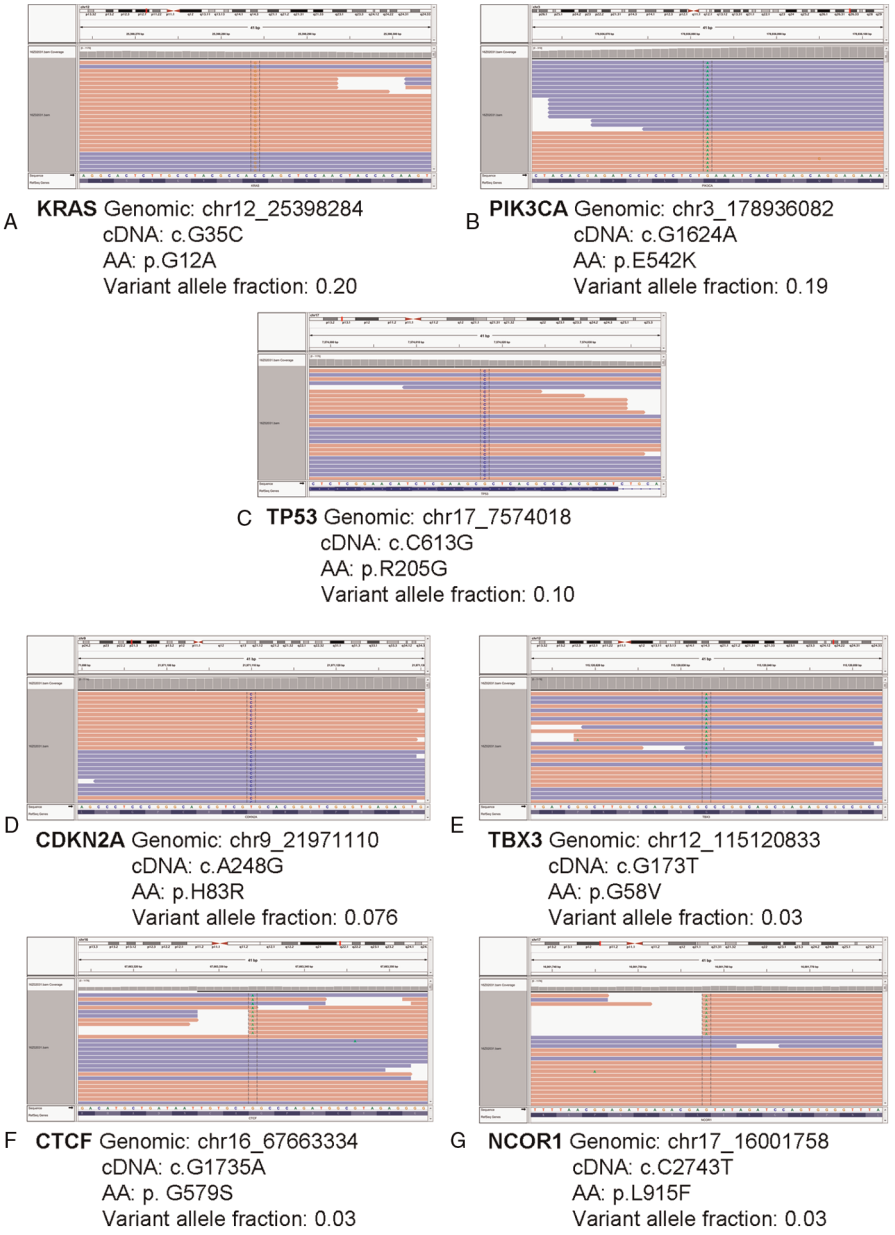

Figure 4. Seven mutant genes, including (A) *KRAS*, (B) *PIK3CA*, (C) *TP53*, (D) *CDKN2A*, (E) *TBX3*, (F) *CTCF*, and (G) *NCOR1*.

erlotinib, afatinibb, and crizotinib have substantially improved the prognosis of selected patients and currently represent the standard first-line treatment of molecularly-defined advanced NSCLC, especially adenocarcinomas.[9,12] However, these therapies offer no obvious benefits for patients with squamous cell carcinoma.[13] Thankfully, immunotherapy strategies, especially immune checkpoint inhibitors, are a major focus of NSCLC research and therapy.[14] Immune checkpoint inhibitors, including monoclonal antibodies directed against cytotoxic T-lymphocyte-associated antigen-4 (such as ipilimumab and tremelimumab) and programmed cell death protein-1/programmed cell death ligand-1 pathway (such as nivolumab and pembrolizumab), have been shown to induce significant and prolonged clinical responses, with a manageable toxicity profile in patients with advanced NSCLC, for both SCC or adenocarcinoma, independently of any somatically activated oncogenes.[13] We believe that as more and more new drugs are developed and applied to clinical practice, the prognosis of patients with lung cancer will get better and better.

Treatment for primary SCC of the tongue, radiotherapy is as effective as surgery in controlling the tumor and is as associated with a lower rate of complications. Treatment for tongue metastasis arising from malignancies is not standardized.[15] When a tongue mass is relatively small, surgical treatment seems effective. However, for larger tumors, surgery at this site sometimes leads to gross morbidity, with such problems as difficulty with swallowing and speech.[16] In the current case, extirpation of the tumor and lymph nodes by dissection or radiation to the tongue lesion may cause severe complications, because the tumor had spread widely from the root of the tongue, and multiple lymph nodes were also involved.

The patient was initially treated with a first-line regimen of doublet chemotherapy with carboplatin and pemetrexed. However, the disease progressed after 2 cycles of chemotherapy, with worsening performance status. We sequenced 127 cancer-related genes from this patient's pathologic specimen, and identified 7 mutant genes, including *KRAS*, *PIK3CA*, *TP53*, cyclin-dependent kinase inhibitor 2A (*CDKN2A*), T-box 3 (*TBX3*), CCCTC-binding factor (*CTCF*), and nuclear receptor corepressor 1 (*NCOR1*) (Fig. 4A–G), but without *EGFR* or *ALK* mutations. This showed no significant differences from patients with metastasis to common sites.[17] KRAS and PIK3CA are in pathways downstream of EGFR, and their mutations induce resistance to EGFR-TKI agents.[18] Current research suggests that *KRAS* mutation is the main driver of poor prognosis in patients with NSCLC, and also may be a common cause of cancer recurrence, but unfortunately, no drugs are available that directly address *KRAS* mutation.[19,20] Mutations leading to the inactivation of *Tp53* had also been shown to be frequent in human lung SCCs, and may lead to expansion of mutant stem cell clones.[21] This would lead to disease progression. We expect that pharmacists can develop targeted drugs for new targets, such as *KRAS* mutation or inactivation of *Tp53* in the near future, so that the treatment of lung cancer can have more choices.

We predicted this patient will not be sensitive to targeted therapy, and will have a poor prognosis. Therefore, we chose to continue systemic chemotherapy for him with paclitaxel and Nida's platinum. He had ongoing soreness at the base of his tongue and died about 7 months after the diagnosis of lung cancer.

References

[1] Zhang H. Apatinib for molecular targeted therapy in tumor. Drug Des Devel Ther 2015;9:6075–81.

[2] Jeba J, Backianathan S, Ishitha G, et al. Oral and gastrointestinal symptomatic metastases as initial presentation of lung cancer. BMJ Case Rep 2016;2016:3488–515.

[3] Terashima T, Matsuzaki T, Kawada I, et al. Tongue metastasis as an initial presentation of a lung cancer. Intern Med 2004;43:727–30.

[4] Mui S, Smith AE. Lingual metastasis as the initial presentation of a large cell lung carcinoma. Otolaryngol Head Neck Surg 1999;121:305–6.

[5] Batsakis JG. The pathology of head and neck tumors: the occult primary and metastases to the head and neck, Part 10. Head Neck Surg 1981; 3:409–23.

[6] Kurt M, Bulut N, Aksoy S, et al. Anterior tongue metastasis from lung cancer. South Med J 2006;99:784–5.

[7] Asamura H. [Revision of TNM Classification for Lung Cancer by Staging and Prognostic Factors Committee of LASLC (International Association for the Study of Lung Cancer)]. Gan To Kagaku Ryoho 2016;43:955–8.

[8] Majumder KR. Carcinoma tongue. Clinicopathol Present 2015;24: 787–93.

[9] Bayraktar S, Rocha-Lima CM. Molecularly targeted therapies for advanced or metastatic non-small-cell lung carcinoma. World J Clin Oncol 2013;4:29–42.

[10] Riely GJ, Yu HA. EGFR: the paradigm of an oncogene-driven lung cancer. Clin Cancer Res 2015;21:2221–6.

[11] Liao BC, Lin CC, Shih JY, et al. Treating patients with ALK-positive non-small cell lung cancer: latest evidence and management strategy. Ther Adv Med Oncol 2015;7:274–90.

[12] Masters GA, Temin S, Azzoli CG, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3488–515.

[13] Santarpia M, Giovannetti E, Rolfo C. Recent developments in the use of immunotherapy in non-small cell lung cancer. Expert Rev Respir Med 2016;10:781–98.

[14] Bílek O, Bohovicová L, Demlová R. [Non-small cell lung cancer—from immunobiology to immunotherapy]. Klin Onkol 2016;29(suppl 4): 78–87.

[15] Ren JJ, Zhao Y, Liu MJ, et al. Langerhans cell sarcoma arising from the root of tongue: a rare case. Int J Clin Exp Pathol 2015;8: 15312–5.

[16] Tsubochi H, Isogami K, Sato N, et al. Successfully treated lingual tonsillar metastasis from bronchial adenocarcinoma. Jpn J Thorac Cardiovasc Surg 2005;53:455–7.

[17] Jang JS, Lee A, Li J, et al. Common oncogene mutations and novel SND1-BRAF transcript fusion in lung adenocarcinoma from never smokers. Sci Rep 2015;5:9755.

[18] Morgillo F, Corte CMD, Fasano M. Mechanisms of resistance to EGFR-targeted drugs: lung cancer. ESMO Open 2016;1:e000060.

[19] Sun L, Zhang Q, Luan H. Comparison of KRAS and EGFR gene status between primary non-small cell lung cancer and local lymph node metastases: implications for clinical practice. J Exp Clin Cancer Res 2011;30:30.

[20] Nagy F, Pongor LS, Szabó A. KRAS driven expression signature has prognostic power superior to mutation status in non-small cell lung cancer. Int J Cancer 2017;140:930–7.

[21] Jeong Y, Hoang NT, Lovejoy A. Role of KEAP1/NRF2 and TP53 mutations in lung squamous cell carcinoma development and radiation resistance. Cancer Discov 2017;7:86–101.

[22] Wu X, Li H, Wang Y, et al. A case report of tongue metastasis from lung carcinoma. Chin J Lung Cancer 2009;11:1217–8.