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CASE IMAGE

WILEY

ALK-rearranged lung adenocarcinoma resistant to alectinib with cauliflower gingival metastasis responds to brigatinib

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To the Editor,

A 71-year-old nonsmoking female was admitted to our hospital with a persistent left gingival mass which had been increasing in size for 2 weeks. The mass had dramatically increased in size, approximately doubling in size in a week, and was accompanied by moderate pain in the left palate gingiva not relieved by oral ibuprofen. Physical examination revealed a cauliflower-like, 3 × 3 cm mass located beside the left upper palate arch near the buccal membrane gingiva (Figure 1(a)). The patient had been diagnosed with advanced lung adenocarcinoma with EML4-ALK fusion 1 year previously. Oral alectinib 600 mg twice a day has been used for almost 1 year and had been well tolerated. Radiological evaluation demonstrated disease progression with an enlarged primary mass and newly diagnosed lung metastasis (Figure 1(c)) compared with the best response to alectinib (Figure 1(b)). No other specific symptoms were reported and blood tests including CEA were almost within the normal range apart from the white blood cell count which was 10.77 × 10^9/l.

Computed-tomography (CT) guided tissue biopsy was performed of the right lung nodule with a subsequent histopathological diagnosis of lung adenocarcinoma (Figure 1(d),

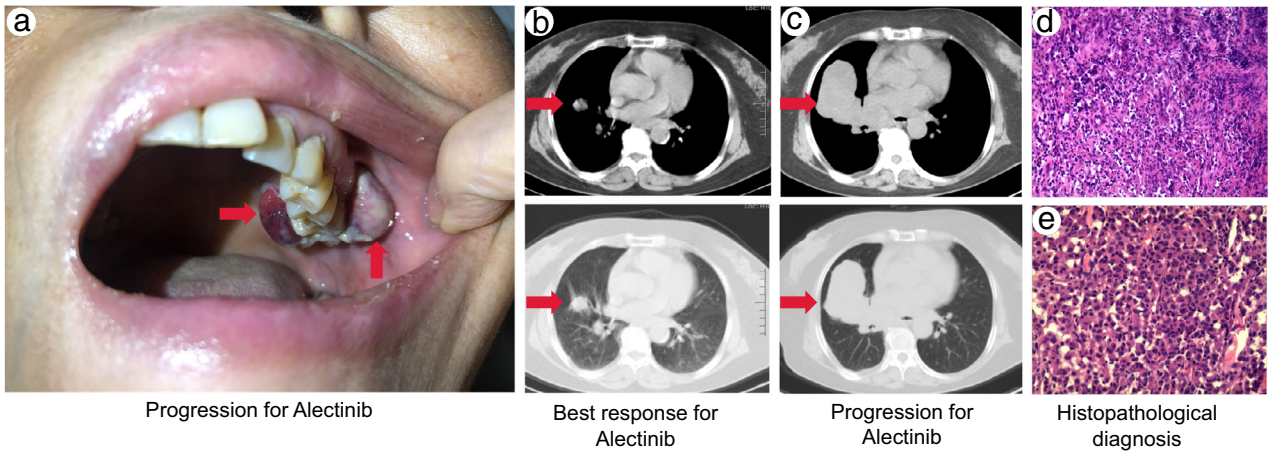
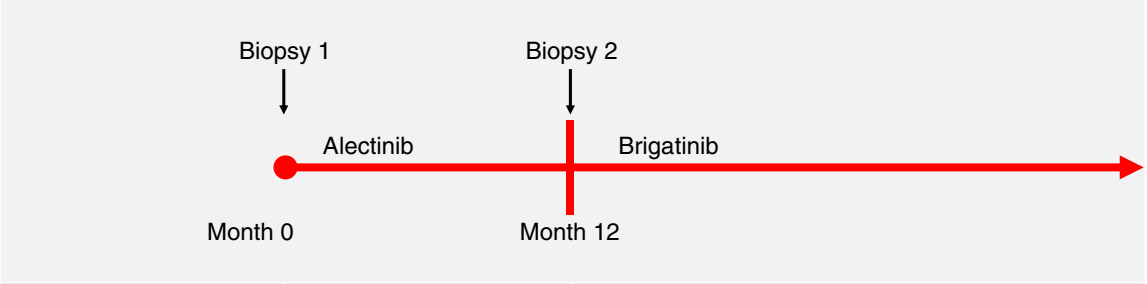


FIGURE 1 (a) The mass was located adjacent to the left upper palatal arch near the buccal membrane gingiva and was approximately 3 × 3 cm in size. (b) The primary tumor, located in the right lung, at its best response to alectinib. (c) Radiological image of primary tumor following progression after treatment with alectinib. (d) Histopathological diagnosis of gingival metastasis and (e) primary lung tumor



	At baseline	Before brigatinib
Samples used	Tissue	Tissue
EML4-ALK (E6:A20)	30.9%	25.7%
ALK p.I1171N	None	27.9%
NF2	None	41.1%

FIGURE 2 The treatment timeline and genotyping analysis

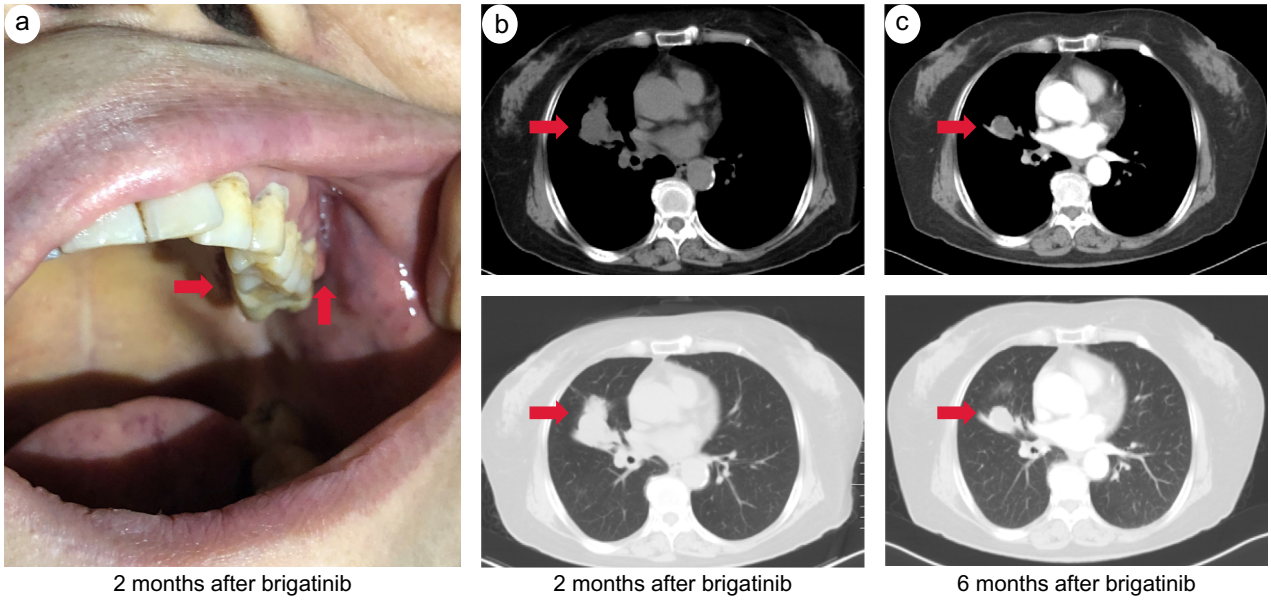


FIGURE 3 Radiological evaluation after 2-months of oral brigatinib for gingival metastasis (a) and lung nodules ([b] 2 months after brigatinib, [c] 6 months after brigatinib). Red arrows indicate the primary and metastatic lesions

CK5/6−, CK7+, Napsin A+, p63-, TTF-1+, ALK+). To further evaluate the pathological diagnosis of the gum lesion, biopsy was performed, and the histopathological diagnosis showed poorly-differentiated adenocarcinoma (Figure 1(e), CK5/6−, CK7+, napsin A+, p63-, TTF-1+, ALK+). Next-generation sequencing confirmed that samples from the primary lung lesion and gum metastasis all harbored EML4-ALK fusion (V3) and I1171T (Figure 2). Gingival metastasis is a rare metastatic site of lung cancer which is generally considered as evidence of widespread disease. According to previous data, the most common cancer types metastasizing to the gingiva are cancer of the kidney, lung, and breast.[1] To our knowledge, this is the first report of a lung adenocarcinoma with palatine-gingival metastasis after progression following alectinib therapy.

Exophytic lesions are the most common clinical manifestations of oral soft tissue metastatic lesions.[2] Most patients with such metastases complain of swelling, pain, and paresthesia. They can easily be confused with primary oral cancers.[3] Pathophysiological lung cancer is characterized by rapid growth and is more aggressive with a tendency towards early lymphatic and blood metastatic spread. We speculate that hematogenous spread could be a mechanism of metastasis for this unusual metastatic tumor.[4] In general, multisite biopsy, pathological identification and NGS are the prerequisites for precise diagnosis and appropriate treatment strategies.

ALK I1171T has been confirmed to be the most common resistance mutation of patients treated with alectinib.[5] Thus, treatment was switched to brigatinib (180 mg once daily with a 7-day lead-in at 90 mg once daily) for this

patient,[6] and a response was obtained for at least 10 months including gingival metastasis (Figure 3(a) for 2 months brigatinib) and lung nodules (Figure 3(b) for 2 months brigatinib, Figure 3(c) for 6 months brigatinib).

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CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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