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Neuroendocrine phenotype as an acquired resistance mechanism in ALK-rearranged lung adenocarcinoma

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ABSTRACT

A 63-year-old caucasian woman, presenting with metastatic primitive lung adenocarcinoma was treated with *ALK* inhibitor crizotinib treatment for six month. After rapid regression of all known lesions, tumor progression appeared six month later on all the already known lesions. A biopsy of subclavicular lymphadenopathy revealed a carcinoma with neuroendocrine phenotype with both immunohistochemical expression of *ALK* protein and *ALK*-rearrangement. It was associated with acquired resistance to crizotinib with *ALK*-rearrangement but without point mutation or amplification of the *ALK* gene.

We herein report the first case of histological neuroendocrine transformation after *ALK* inhibitor crizotinib treatment, associated with acquired resistance to crizotinib.

1. Introduction

About 4% of patients with non-small cell lung carcinoma (NSCLC) have a chromosomal rearrangement involving the *ALK* (anaplastic lymphoma kinase) gene at 2p23 that usually generates a fusion gene between *EML4* (echinoderm microtubule-associated protein-like 4) which results in constitutive kinase activity that contributes to carcinogenesis and drives the malignant phenotype. The discovery of *ALK*-rearrangement in a subset of NSCLC [1] has led very rapidly to the validation of *ALK* inhibitor crizotinib by a phase III trial in which patients were enrolled on the basis of a positive break-apart FISH assay [2]. Besides *EML4*, other translocation partners have also been identified in NSCLC, notably kinesin family member 5B (*KIF5B*), TRK-fused gene (*TFG*) and kinesin light chain 1 (*KLC1*), leading to signaling pathway activation and both experimental and clinical responses to crizotinib. Crizotinib is an anti-cancer drug acting as an *ALK* and *ROS1* (c-ros oncogene 1) tyrosine kinase inhibitor and has also been approved for treatment of non-small cell lung carcinoma (NSCLC) displaying *ROS1* rearrangements [3]. Crizotinib resistance arises through various mechanisms including on the one hand new alterations/mutations and developments which maintain the dominance of *ALK* in the biology of the tumoral cell, on the other hand the emergence of either oncogeniques abnormalities (*EGFR* or *KRAS*) which come replace the dominant role of *ALK*. We report here the first case of histological neuroendocrine transformation associated with acquired resistance to crizontinib.

2. Case report

In April 2013, a 63-year-old caucasian woman with no smoking history presented with neurologic troubles. Computed Tomography (CT) revealed brain metastasis, with mediastinal and left subclavicular lymph adenopathy and a nodule of the right lower pulmonary lobe (Fig 1A–C). CT-guided lung biopsy revealed a primary pulmonary invasive acinar adenocarcinoma according to the criteria of the latest edition of WHO classification [4], with immunohistochemical expression of *ALK* protein (mouse monoclonal antibody, 5A4, Abcam, Cambridge, UK). There was no immunohistochemical expression of TTF-1, chromogranin and synaptophysin (Fig.1D, F and H). Mitotic count was 3.4 mitoses/mm^2. The proliferative index evaluated with ki67

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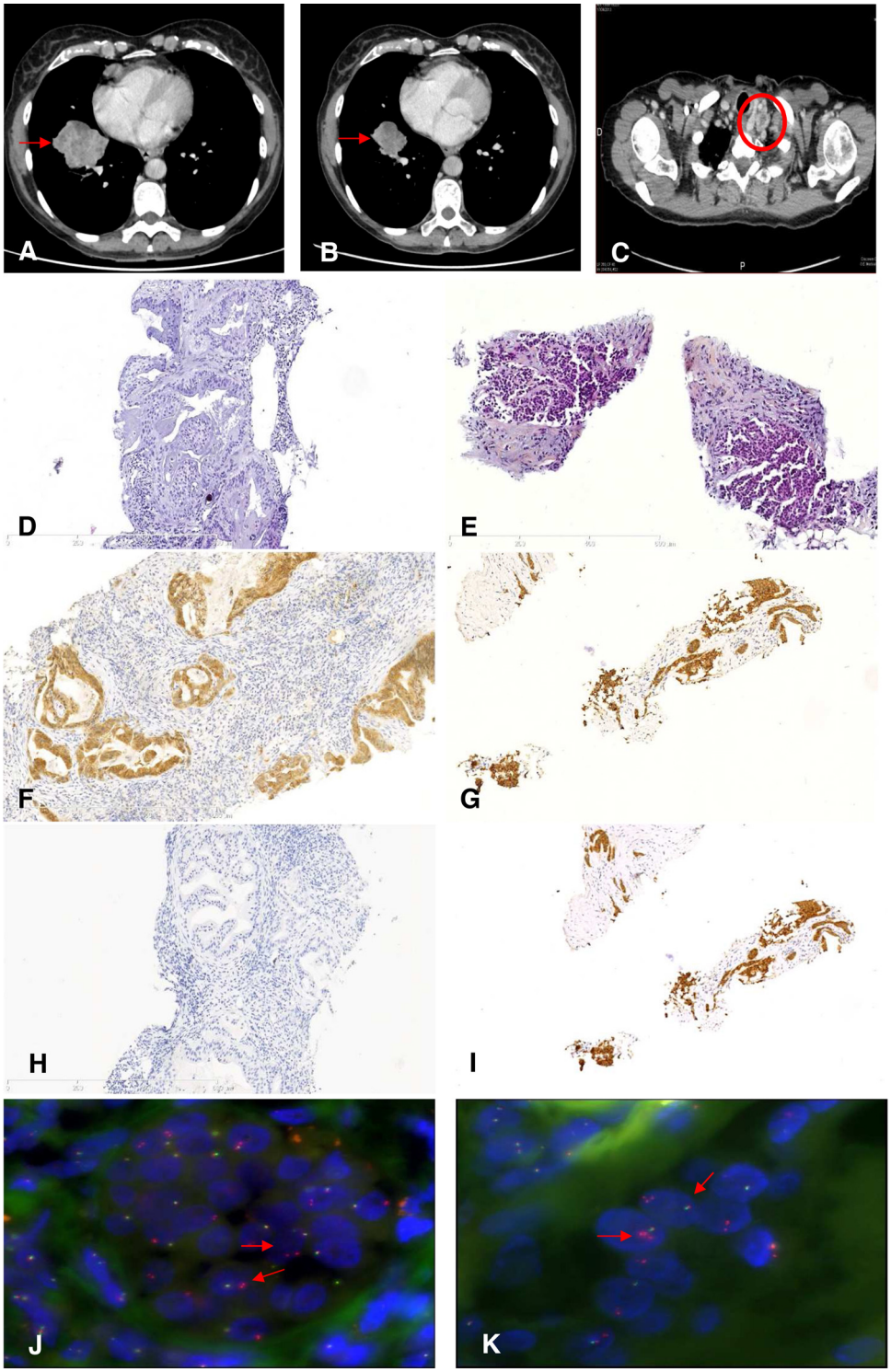

Fig. 1. Computed Tomography (CT) at baseline (A–C), histopathological features of the transthoracic inferior lobe biopsy before treatment (D, F, H and J) and of the subclavicular biopsy after crizotinib therapy (E, G, I and K).
A: Computed Tomography (CT) at baseline before crizotinib 2013/08.
B: CT showing tumor regression under crizotinib 2013/11.
C: CT showing subclavicular lymph node progression at the time of rebiopsy 2014/02.
D and E: Hematein-eosin stained sections show adenocarcinoma morphology with glandular formations at time of diagnosis (A) while neuroendocrine pattern with solid nests and trabeculae is observed after crizotinib treatment at time of progression (C).
F and G: Strong ALK immunoreactivity in both samples obtained with the ALK(5A4) (Abcam) primary antibody.
H and I: Lack of immunoreactivity for chromogranin at time of diagnosis (H) and strong chromogranin expression on subclavicular biopsy sample at time of progression (I).
J and K: FISH analysis with a break-apart ALK probe (Abbott) showing the presence of a similar pattern in both samples with a predominant 1 Red 1 Fusion pattern (arrows). Rare cells (less than 10%) display 2–4 extra-Red signals without reaching amplification threshold. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)