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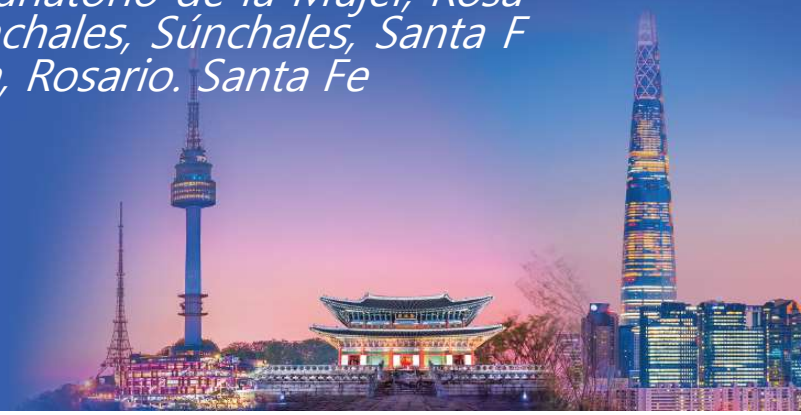
Transformation to Small Cell Lung Cancer from an Adenocarcionma Egfr+ as Resistance Mechanism. Utility of Liquid Biopsy in Treatment Selection

AUTHORS: MUÑOZ Miguel[1,2,3] POSSI, Beatriz[2]; SUAREZ, Lucia[2]; SABATINI, Luciana[1]; DASCANIO, Muriel[1]; PALASI Jorge [1]; PERROUD, Herman[1,3].

1- Unidad de genómica y medicina de precisión. Sanatorio de la Mujer, Rosario, Santa Fe, Argentina; 2- Centro Oncológico Súnchales, Súnchales, Santa Fe, Argentina. 3- Universidad Abierta Interamericana, Rosario. Santa Fe



Introduction

- The advent of target therapies for the growth factor receptor (EGFR) pathway revolutionized the treatment of NSCLC. EGFR is a member of the HER family, which also includes HER2 (ErbB2), HER3 (ErbB3), HER4 (ErbB4). When the extracellular domain of EGFR binds to its ligands, it generates a signal that regulates multiple cellular processes, including survival, and apoptosis.
- Constitutive activation of EGFR signaling, caused by genetic shocks or by gene amplification or both, has been shown to be closely connected with the initiation, progression, and poor prognosis of NSCLC.
- The two most common EGFR activators are exon 19 deletions (E746-A750del) and exon amino acid substitution (L858R), collectively accounting for >90% of EGFR activators. These two alterations are the best characterized mutations that resist sensitivity to EGFR-tyrosine kinase inhibitor (EGFR-TKI) therapies, resulting in high response rates (up to 70%) and longer median survival (up to 24- 30 months) than in wild-type EGFR patients (WT).
- However, numerous pathways of resistance to EGFR TKIs have been detected, such as the appearance of secondaries (T790M, C797S), activation of alternative sensing pathways (Met, HGF, AXL, Hh, IGF-1R), sensing of the activation cascade (AKT mutations, PTEN loss), impairment of the EGFR-TKI mediated apoptosis pathway (BCL2-like deletion 11/BIM polymorphism) and histological transformation.

Clinical Case

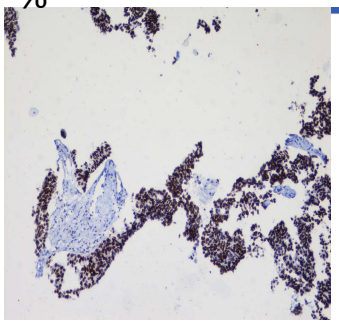
- **CLINICAL CASE**: 51-year-old, former tobacco user, diagnosed in 2013 with left locally advanced lung adenocarcinoma, Stage IIIB, EGFR mutated (L858R) by liquid biopsy (LB) because the lake o f histological material was not enough to study EGFR in tumoral tissue. Initially received gefitinib 250 mg/day. After 4 years she progressed in 2017, with increase of lung tumor mass with bone compromise. The histological diagnose of lesion showed: Poorly differentiated lung carcinoma w ith features of SCLC confirmed by Immunohistochemistry, a 2nd LB was performed and informe d EGFR L858R mutation in circulating DNA (cDNA). The therapeutic plan was Radiation therapy i n rib cage and 6 cycles of chemotherapy platin based plus etoposide, after complete treatment response assessment (RA) showed stable disease. In March 2019 a 3rd LB was performed, an EG FR L858R + in cDNA was still present; so patient restart Gefitinib.

Clinical Case

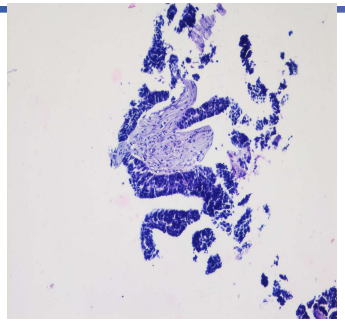
- A 6-month tomography control informed stable lung images with new liver metastases and a br ain CT scan performed because neurological symptoms showed a right frontal cortical lesion of 16 mm x 19 mm. She received whole brain radiotherapy. She archived complete response in CN S by images and significant clinical improvement, but progression, with multiples nodules in the lung and liver. The new liver biopsy demonstrated an infiltration of SCLC, and a 4th LB showed E GFR + L858R mutation. Based in this information it was decided to continue with gefitinib and s tart a second line chemotherapy, with taxanes, in a concurrent way. At the moment of this repor t, the patient is still alive with stable disease, after three cycles of chemotherapy, without any se vere adverse effects, except mild diarrhea and dermatitis.

SECOND HISTOLOGY BIOPSY INMUNO HISTOCHEM ESTRY:

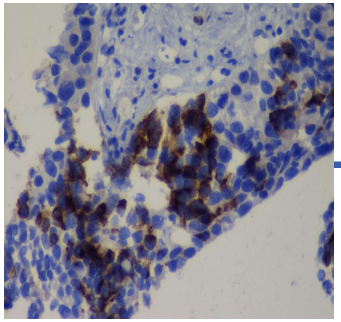
Citoqueratine +; TTF-1 +; Cromogranine +; Ki 67:70 %



TTF

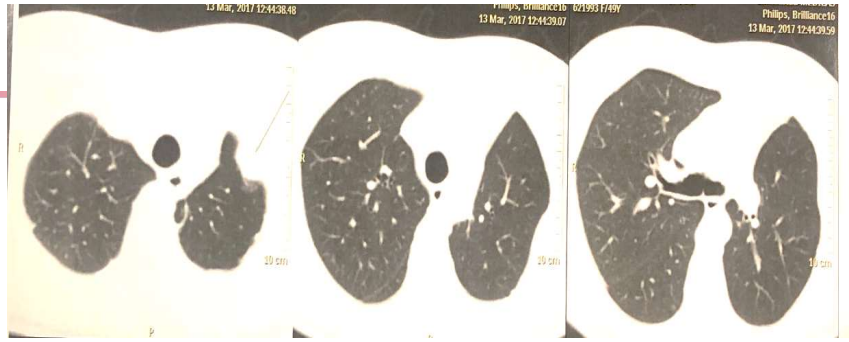


HEMATOXILINE

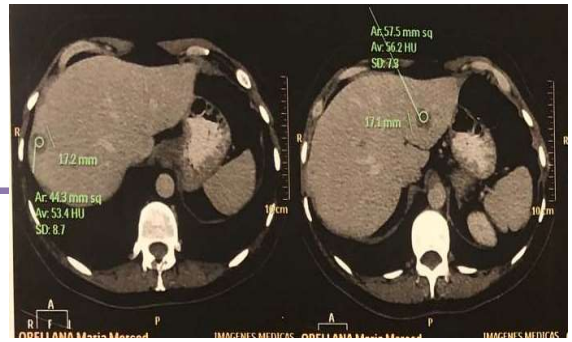


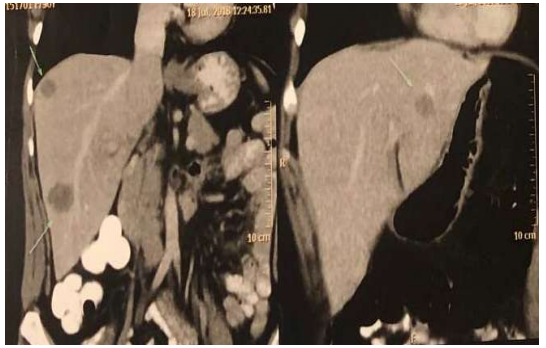
CROMOGRANINE

FIRST CT SCAN: Lung adenocarcinoma



RELAPSE CT SCAN: Small Cell Lung Cancer





CONCLUSIONS

LB has demonstrated in this patient the coexistence of L858 Mutation in blood and SCLC in tumor tissue. The transformation to SCLC in histological tissue biopsy is a very rare m echanism of resistance to TKIs, about 3 % of the cases of the patients with EGFR mutatio ns. LB allows us to select the best treatment for this patient and could detect the absenc e of other mechanism of resistance, like mutation of the EGFR T790M. At the moment of the presentation of this abstract, there are very few cases and reports about the right tr eatment of the patient with this uncommon condition in the literature. One of this repor ts describe a patient with the T 790 M in LB and a transformation to SCLC in tumor tissu e, treated with osimertinib plus chemotherapy. A larger number of patients could provid e a strong evidence on this issue.