An EGFR-mutant lung adenocarcinoma that transformed into small-cell lung cancer. A case report

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Background. Transformation of EGFR (epidermal growth factor receptor) – mutant non-small cell lung cancer (NSCLC) into small-cell lung cancer (SCLC) is one mechanism of resistance to tyrosine kinase inhibitor (TKI) treatment, seen in approximately 3–10% cases. Such transformed SCLC often retains the original EGFR mutation (EGFRM), which is not otherwise observed in SCLC.

Case report. We present a 67 y/o woman with pulmonary adenocarcinoma (AC) and EGFRM deletion on exon 19. After initial treatment with whole brain radiotherapy and 7 months of TKI afatinib, progression was observed. Liquid biopsy detected deletion on exon 19 and T790M mutation. Chemotherapy carboplatin plus pemetrexed was administered, with no response. Genetics from a rebiopsy of lung revealed deletion on exon 19. After 12 months treatment with TKI osimertinib, a progression in lung and pancreas lesions was detected, docetaxel was used, with followig progression. The lung biopsy revealed SCLC. Significant elevation of serum markers carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) was observed at the time of the SCLC diagnosis. Treatment with carboplatin and etoposide was not effective. The next biopsy found two populations of cells: SCLC and AC. The biopsy from the pancreatic lesion revealed metastasis of SCLC. PCR confirmed EGFRM deletion on exon 19 in the lung SCLC tissue sample. The following treatment lines of topotecan, erlotinib were not effective. The patient survived 36 months from diagnosis, 7 months from detection of SCLC.

Conclusion. Screening for transformation of EGFR-mutant NSCLC to SCLC should be considered in resistance to TKI. In the presented case, this rare transformation was confirmed by histopathologic examination and by PCR. EGFRM in the lung SCLC, identical to that found in the original lung AC, was detected. Further, the observed elevation of serum tumor markers NSE and CEA can indicate this infrequent transformation and help to decide on rebiopsy.

Key words: EGFR mutation, non-small cell lung cancer, small-cell lung cancer, transformation

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INTRODUCTION

Mutations of EGFR (epidermal growth factor receptor) occur in 10–15% of non-squamous non-small cell lung cancer (NSCLC) in Caucasian populations, and are more common in Asian populations, up to 50%. EGFR mutations (EGFRM) are found mainly in adenocarcinomas, more often in women and non-smokers. Three generations of tyrosine kinase inhibitors (TKIs) are available as standard for the treatment of EGFR-mutant advanced NSCLC. The effect of TKI lasts on average one to two years, before the disease progression and resistance to treatment develop.

In first- and second-generation TKIs, the acquired resistance is mediated in about 60% of cases by the secondary EGFR mutation T790M. Other mechanisms are HER2 amplification, MET amplification, transformation into small-cell carcinoma (SCLC), epithelial-to-mesenchymal transition (EMT), PIK3CA mutation, BRAF mutations, and about 15% are due to the unknown mechanisms[1]. Third-generation TKIs are effective for the T790M mutation, so the mechanisms of resistance are different and there is no one dominant. These include MET amplification, HER2 amplification, EGFR amplification, transformation into small-cell or squamous cell carcino-

ma, EGFR mutation C797X, fusions of ALK, RET and BRAF, mutations of KRAS and others[2].

A transformation of EGFR-mutant NSCLC into small-cell lung cancer is one of the mechanisms of resistance to TKIs of all generations, seen approximately in 3–10% cases[3-4]. Such a transformed SCLC is different from the regular SCLC. It is found in non-smokers, and often retains EGFRM. More than two thirds of EGFRM are exon 19 deletions, but only very rarely is T790M present[5]. In addition to EGFRM there is always loss of genes TP53 and RB1 in the original NSCLC and in the transformed SCLC (ref.[6]). The transformation occurs 13–18 months after the start of TKI treatment[5,7]. The diagnosis of such transformed SCLC is possible only from a tissue biopsy, not liquid biopsy (ctDNA). The "transformed" and "classic" SCLC have similar sensitivity to chemotherapy using platinum plus etoposide. There is a response in about 50% to 80% (ref.[7-8]). Chemotherapy is sometimes administered concomitantly with TKI, especially if both cell clones are present[7]. Prognosis is similar, median overall survival is 10–11 months after the onset of SCLC. The largest group of patients studied is about 70 patients[7].

CASE REPORT

A 67-year-old woman, non-smoker, presented with symptoms of headache, nausea and mild cough. The family history was unremarkable. Scans revealed central lung cancer with mediastinal lymphadenopathy, small fluidothorax, and numerous brain metastases. At the time of the diagnosis, the pancreas was atrophic, with cysts, without signs of metastases. Bronchoscopy and transbronchial biopsy from the left lower lobe bronchus (LLB) confirmed TTF1+ pulmonary adenocarcinoma (AC) in October 2018. Genetic analysis revealed EGFRM of deletion type on exon 19. After whole brain radiotherapy (WBRT), TKI afatinib was introduced, with good response. After 7 months of afatinib treatment a progression in mediastinum and pancreas was observed. We performed a liquid biopsy and detected deletion on exon 19 and T790M mutation. Osimertinib was not available, so four cycles of chemotherapy with carboplatin plus pemetrexed were administered, with no response. On CT scans we could see a progression of atelectasis in the lower left lobe – indirect signs of the tumor progression, and newly differentiated osteolytic metastastis in the sixth rib on the right with a pathological fracture. Rebiopsy from LLB confirmed AC, genetics from biopsy revealed deletion on exon 19 (and no T790M) (Fig. 1). Then osimertinib was introduced, response was achieved. After 12 months of osimertinib treatment a progression in lung and pancreas was detected. The next, fourth line of treatment with 4 cycles of docetaxel was used, with following progression. The biopsy from LLB found SCLC (Fig. 1). Subsequent treatment with carboplatin and etoposide was not effective. The next biopsy from LLB found two populations of cells: SCLC and AC (Fig. 1). Biopsy from pancreatic lesion revealed metastasis of SCLC (Fig. 1). PCR confirmed EGFRM deletion on exon 19 in the lung SCLC tissue sample. The next treatment with topotecan was not effective. Erlotinib was started in September 2021, without any effect. The patient survived 36 months from the diagnosis of EGFR-mutant NSCLC, 7 months from the detection of SCLC.

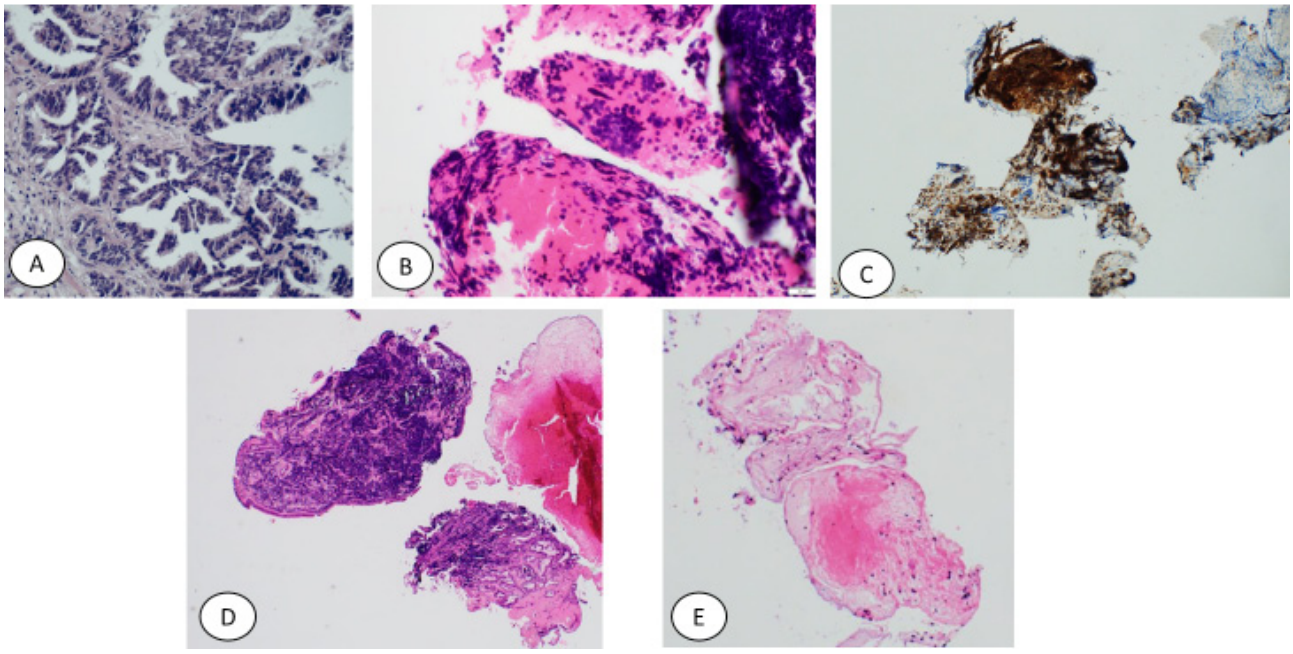
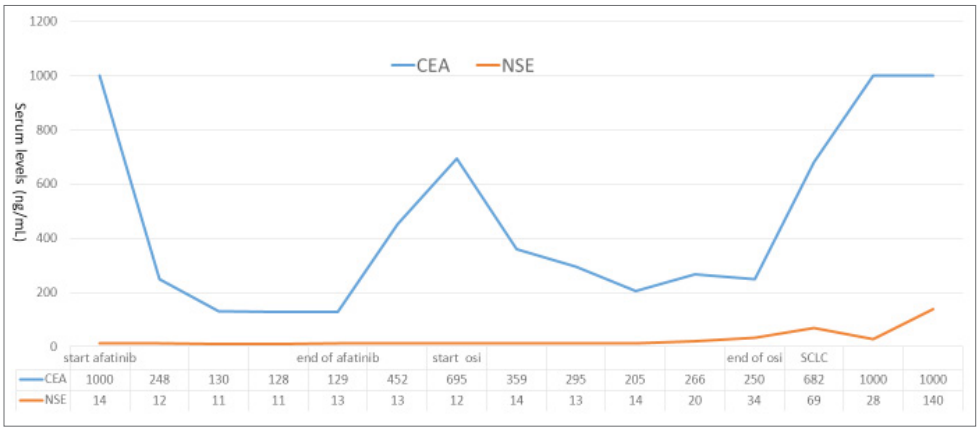


Fig. 1. Histopathologic findings. **A.** Adenocarcinoma in lung, before the treatment with osimertinib, biopsy in 11/2019. **B.** small-cell lung carcinoma in lung, after treatment with osimertinib and afterwards docetaxel, biopsy 2/2021 (H & E). **C.** Immunohistochemical staining for synaptophysin in small-cell carcinoma in lung, after treatment with osimertinib and afterwards docetaxel, biopsy 2/2021. **D.** Two populations of cells: adenocarcinoma and small-cell lung carcinoma in lung, after treatment with carboplatin and etoposide, biopsy 6/2021 (H & E). **E.** small-cell lung carcinoma in pancreatic metastasis, biopsy 7/2021 (H & E).



CEA	1000	248	130	128	129	452	695	359	295	205	266	250	682	1000	1000
NSE	14	12	11	11	13	13	12	14	13	14	20	34	69	28	140

Fig. 2. Serum tumor markers levels (ElectroChemiLuminescence immunoassay, Cobas E411): carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) during the course of treatment with subsequent lines of afatinib, carboplatin plus pemetrexed, osimertinib (osi), docetaxel, carboplatin plus etoposide, topotecan, erlotinib.

Tumor markers carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) were monitored during the whole course of the treatment. Significant elevation of NSE and CEA was observed at the time of the diagnosis of transformed SCLC (Fig. 2).

DISCUSSION

A patient with EGFR-mutant lung adenocarcinoma with an activating mutation deletion on exon 19, and later with acquired T790M mutation, and with brain metastases treated with WBRT at the time of the diagnosis, received systemic treatment with the sequence afatinib – chemotherapy with platinum – osimertinib. She achieved progression-free survival (PFS) 24 months with this sequence treatment. Afatinib treatment lasted less than expected, only 7 months, and it was caused by early development of resistant EGFR mutation on exon 20 T790M, detected in liquid biopsy. Osimertinib was not used in the second line because of not being covered by health insurance at that time. The second line with carboplatin and pemetrexed was used, with no response. Genetic analysis from rebiopsed lung tumor revealed deletion on exon 19 and no T790M, which is interesting. This can be explained by a loss of T790M after chemotherapy or by suboptimal analytic method. The second reason is more probable. The genetic analysis was performed by system cobas® EGFR Mutation Test v2, which is known for lower sensitivity for T790M mutation. Osimertinib was used in the third line with success, PFS lasted for 12 months, longer than afatinib in the first line. Osimertinib is efficient in T790M-mutated lung cancer.

The second rebiopsy from LLB revealed SCLC. At that time the patient had completed two lines of TKI and two lines of chemotherapy. The transformation of NSCLC to SCLC might be explained either by a phenotypic switch from NSCLC to SCLC or by the combination of SCLC and adenocarcinoma that had been present from the baseline, with SCLC becoming the main component after the treatment[9]. The first possibility, the real transformation of EGFR-mutant lung adenocarcinoma to SCLC is proven by the finding of EGFR mutation in the sample of SCLC. EGFRM in SCLC was identical with EGFRM in lung adenocarcinoma. This was deletion on exon 19. This type of mutation is the most frequent mutation found in transformed SCLC (ref.[10]). T790M mutation is almost never found in transformed SCLC, as it was the case in our patient[9]. Generally, EGFR mutations don´t occur in SCLC.

Chemotherapy with carboplatin plus etoposide, the standard treatment in SCLC, had no effect on the transformed SCLC in our case. The previous administration of two lines of chemotherapy (carboplatin plus pemetrexed, then docetaxel) before the diagnosis of transformed SCLC, could be a partial explanation, as the chemo-resistant clones could prevail.

The strength of this case report is in the serial biopsies. After targeted and chemotherapy treatment, the transformed small-cell carcinoma, later the mixed small-cell carcinoma plus adenocarcinoma from the lung tumor and afterwards the small-cell carcinoma from metastasis in the pancreas were histologically verified.

Measurement of the serum tumor markers such as CEA and NSE, and monitoring them during treatment of NSCLC are not considered a standard of care, but they are a cheap and readily available method, in contrast to biopsies and DNA analysis. They can be useful in the diagnosis of small-cell carcinoma, as it was in our case[11].

CONLUSION

The possibility of transformation EGFR-mutant NSCLC to SCLC after TKI treatment should be taken into account. It is a rare mechanism of resistance to EGFR TKIs, but SCLC has well defined treatment with specific chemotherapy. In the presented case this transformation was confirmed in the lung biopsies after 26 months of treatment with two lines of TKI (afatinib, later osimertinib) and chemotherapy. We also confirmed the

pancreatic SCLC metastasis. PCR detected the EGFRM in lung SCLC, identical with that of primary lung AC, it was deletion on exon 19. At the time of diagnosis of SCLC, a significant elevation of serum tumor markers CEA and NSE were detected. Significant elevation of tumor markers, in particular NSE, can indicate an infrequent transformation EGFR-mutant NSCLC to SCLC, and an invasive procedure – rebiopsy can be warranted.

Author contributions: GC: care for the patient, manuscript writing; DO: manuscript writing and revision; GK: care for the patient, manuscript revision; LP: histopathological examination, manuscript revision; AF: genetic analysis, manuscript revision; MS: histopathological examination, manuscript revision; DJ: radiological examination, manuscript revision; PB: care for the patient, manuscript revision.

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