

# Histologic Transformation in an EGFR-Mutant Lung Cancer in a Filipino Patient Treated with Afatinib: Case Report and Review of Literature

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## ABSTRACT

We report a case of a 64-year-old Filipino male who initially presented with chronic cough, easy fatigability, and weight loss. Work-ups lead to a diagnosis of lung adenocarcinoma with epidermal growth factor receptor (EGFR) exon 19 deletion. Patient was placed on targeted therapy with Afatinib. He was able to complete 17 months of targeted therapy with relatively stable disease before experiencing recurrence of easy fatigability. Work-ups then lead to a diagnosis of a high-grade neuroendocrine tumor consistent with small cell lung carcinoma (SCLC). Afatinib was then discontinued and the patient was started on Carboplatin and Etoposide. However, after only one cycle, the patient's symptoms progressed and the patient eventually expired. Histological transformation of EGFR-mutant adenocarcinoma to SCLC as a mechanism of resistance to targeted therapy has been documented in literature since 2006. However, to our knowledge, this is the first fully-documented case of histologic transformation occurring in a Filipino patient. As molecular targeted therapy and immunotherapy become standard-of-care in our country, it is of paramount importance that clinicians and pathologists are aware of the various mechanisms of resistance that can occur as a result of these treatments.

*Key words: Lung cancer; adenocarcinoma; small cell carcinoma; receptor; epidermal growth factor; cell transformation, neoplastic*

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## INTRODUCTION

Lung cancer is still one of the major causes of cancer-related deaths worldwide. In recent years, the advent of molecular targeted therapy has drastically changed the treatment and prognosis of these patients. Herein we present a case of a 64-year old Filipino male with an Epidermal Growth Factor Receptor (EGFR)-mutant lung adenocarcinoma, which was treated with a tyrosine kinase inhibitor (TKI; Afatinib) and subsequently developed small cell carcinoma on progression.

## CASE

We report a case of a 64-year-old Filipino male who initially presented with complaints of chronic cough associated with easy fatigability and weight loss. He had a 30-pack-year smoking history along with controlled hypertension and diabetes mellitus type 2. Family history was significant only for breast cancer. Physical examination showed decreased breath sounds at the right lung base. Chest x-ray revealed a hazy density at the right infraclavicular region and in the right lung base, which prompted further evaluation. Chest CT scan showed a right upper lobe nodule measuring 2 cm in widest diameter, innumerable bilateral pulmonary parenchymal and fissural nodules, an enlarged precarinal lymph node, and right-sided pleural effusion. There were no enlarged mediastinal or hilar lymphadenopathies. Upper abdomen CT scan, total body bone scan, and brain MRI were all negative for metastasis. CT-guided biopsy of the right lung nodule and thoracentesis of the right pleural effusion were done in another institution. Histopathology



of the right lung nodule showed lung adenocarcinoma while that of the pleural fluid showed adenocarcinoma. Immunohistochemical (IHC) stains were done on both specimens, showing positive staining for CK7 and TTF-1 and negative staining for CK20, CK5/6 and calretinin. Epidermal growth factor receptor (EGFR) mutation analysis using real-time polymerase chain reaction (real-time PCR) showed exon 19 deletion.

While awaiting results of EGFR, the patient was given first line metastatic treatment with chemotherapy using Pemetrexed and Carboplatin, which he completed for 6 cycles. Re-evaluation CT scans of the chest showed stable disease on the lung nodules. The patient was subsequently started on Afatinib. He was able to complete 17 months of targeted therapy with relatively stable disease, before again experiencing easy fatigability.

On work-up, re-evaluation CT scan of the chest showed an interval progression in the size and number of the multiple, confluent, non-calcified, pleural-based and parenchymal pulmonary nodules and masses in the right lung. The largest mass had a diameter of 12.5 cm. These findings prompted CT-guided fine needle aspiration biopsy of the right lung mass at our institution.

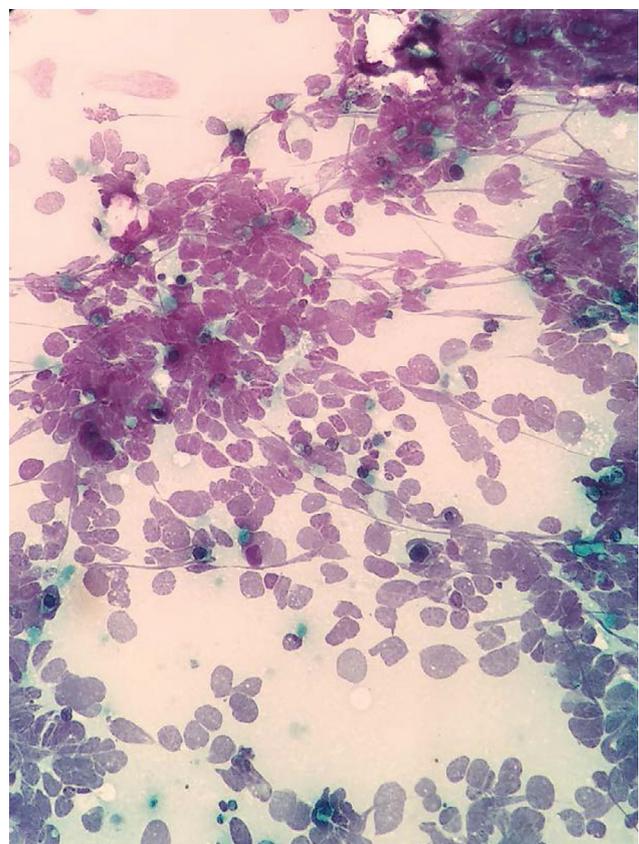
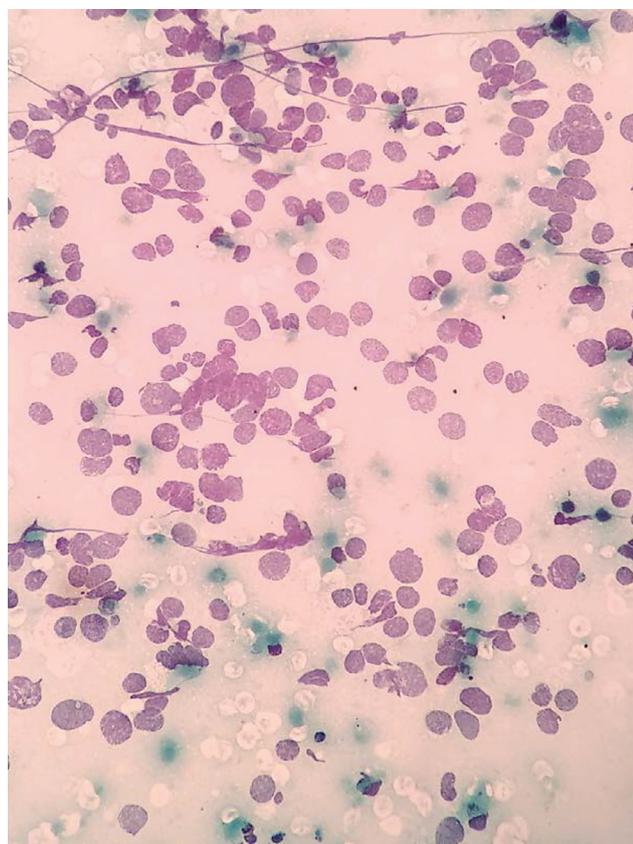
The moderately cellular smears and cell block showed atypical cells with large, round, hyperchromatic nuclei, inconspicuous nucleoli and scant cytoplasm. These were seen scattered singly and arranged in tight clusters and

in monolayered sheets (Figure 1). Nuclear molding was also appreciated on the cell block. Immunohistochemical studies revealed that these atypical cells were positive for TTF-1, synaptophysin, and CD56, and focally positive for chromogranin A (Table 1; Supplemental Figure 1). Ki-67 was high at more than 90%. The case was then signed out as a high grade neuroendocrine tumor, consistent with small cell carcinoma.

**Table 1.** Immunohistochemical stain results of the patient's right lower lobe pulmonary mass

Immunohistochemical Stain	Result
TTF-1	Positive
Synaptophysin	Positive
Chromogranin A	Positive, focal
CD56	Positive
Ki-67	> 90%

The specimen was also sent for EGFR mutation analysis and results showed the patient's original exon 19 deletion. PD-L1 was performed and showed a tumor proportion score of less than 1%. Afatinib was then discontinued and chemotherapy with Carboplatin and Etoposide was planned in October 2018. However, the patient continued to be symptomatic at this time with shortness of breath and episodes of desaturation. There was also concomitant pneumonia. He was given only one cycle of Carboplatin and Etoposide before his symptoms progressed. The patient eventually expired.



**Figure 1.** Fine needle aspiration biopsy of the patient's right lower lobe pulmonary mass. The smears showed atypical cells with large, round, hyperchromatic nuclei and scant cytoplasm. These were seen scattered singly and arranged in tight clusters. (Papanicolaou stain, 400X).

## DISCUSSION

The biopsy that demonstrated small cell carcinoma may represent any of three possibilities: (1) a new primary; (2) combined small cell carcinoma with adenocarcinoma; and (3) histologic transformation of adenocarcinoma to small cell carcinoma as a mechanism of resistance to targeted therapy with tyrosine kinase inhibitors.

The existence of combined-histology lung cancers has been recognized and documented in large case series.<sup>1,2,3</sup> However, such cases usually constitute only a small proportion of small cell lung carcinomas (SCLC). The initial diagnosis of pure non-small cell lung carcinoma (NSCLC) on biopsies in these cases may be due to the limited material submitted at initial diagnosis, which may not be representative of the entire tumor.<sup>4</sup> Another possibility is that the SCLC component of these mixed tumors become more prominent after regression of the adenocarcinoma component in response to EGFR inhibitors.<sup>5</sup>

Erlotinib, gefitinib, and afatinib are three EGFR inhibitors that are widely used for the first-line treatment of lung cancers with EGFR-activating mutations. However, resistance to these inhibitors develops after an average time of 12 months.<sup>4</sup> This is concordant with data from a 2017 case series done in Malaysia.<sup>6</sup> In this case, resistance developed after 17 months of afatinib therapy, as evidenced by the increase in the number and sizes of the pulmonary and pleural-based nodules on imaging studies.

There are several mechanisms that may account for the development of resistance in tumors that have been treated with tyrosine-kinase inhibitors. These can be generally divided into two main categories: (1) primary or intrinsic resistance and (2) secondary or acquired resistance.

In primary resistance, there is an immediate inefficacy to EGFR-TKI. This is often attributed to a non-sensitive EGFR mutation, such as an exon 20 insertion that adds residues at the N-lobe of EGFR (M766 to C775).

In contrast, secondary or acquired resistance is defined by an initial response to EGFR-TKI with stable disease and the subsequent development of progression. The mechanisms of acquired resistance can be divided into three: (1) insurgence of secondary mutations in the EGFR gene, such as exon 20 T790M; (2) activation of alternative pathways that bypass the need for EGFR signalling; and (3) phenotypic or histologic transformation.<sup>7</sup> Of these, the T790M mutation is the most commonly documented mechanism, accounting for 50-60% of cases.<sup>4</sup> Histological transformation to SCLC is the least common mechanism, occurring in 3-10% of EGFR-mutant NSCLCs.<sup>8</sup> It should be noted however, that the aforementioned mechanisms are not mutually exclusive; thus, a combination of the mechanisms may occur in the same patient.<sup>5</sup>

In the case presented in this report, the original EGFR exon 19 deletion was identified in the biopsy that showed small cell carcinoma. This finding effectively rules out the possibility of a new primary and favors that the prior adenocarcinoma on initial diagnosis is related to the small cell carcinoma. While there is the possibility that

the patient's tumor is of mixed histology right at the outset, given that the diagnosis of adenocarcinoma was based merely on biopsy material and not on a resection, it is believed that combined small cell carcinoma and adenocarcinoma would have a less dramatic response to EGFR inhibitors and would develop resistance much earlier during the course of treatment.<sup>4</sup> In our case, the patient had stable disease for 17 months while he was on Afatinib therapy. Thus, given the clinical course of this patient, histologic transformation of adenocarcinoma to small cell carcinoma is the favored mechanism of resistance that developed in this tumor.

Histological transformation of EGFR-mutant adenocarcinoma to SCLC was first documented in 2006 in a 45 year old woman who had EGFR-mutant adenocarcinoma and who was subsequently treated with erlotinib for 18 months.<sup>9</sup> Other case series have since demonstrated this occurrence, with the transformation to SCLC supported by histomorphology, positive immunohistochemical staining for synaptophysin, chromogranin, or NCAM, and/or retention of the tumor's original EGFR-activating mutation.<sup>3,4,6,8,10,11,12,13,14</sup> Current data suggest that histological transformation to SCLC can occur in up to 14% of EGFR-mutant NSCLC as a mechanism of tyrosine kinase inhibitor resistance.<sup>12</sup> In Asia, a case series done in Shanghai enrolled 87 patients whose lung adenocarcinomas transformed to SCLC after TKI treatment.<sup>15</sup> Among these patients, female gender and EGFR exon 19 deletion were found to be independent positive predictors for SCLC transformation.<sup>15</sup> In contrast, the patient in this case report is male with an EGFR exon 19 deletion.

Genomic analyses have shown that *RBI* inactivation is a necessary step in SCLC tumorigenesis. Among patients with EGFR-mutant adenocarcinoma that transformed to SCLC, 100% had loss of *RBI*, suggesting that this inactivation is a vital step in transformation from adenocarcinoma to SCLC.<sup>4</sup> In this case, however, testing for *RBI* inactivation was not performed. Other steps in this transformation pathway remain to be elucidated, but studies have suggested that the PI3K-AKT pathway also plays an important role in SCLC transformation.<sup>5</sup>

The cells of origin of SCLC and adenocarcinoma have traditionally been thought to be neuroendocrine cells and alveolar type II cells, respectively. However, studies done on murine models of lung cancer suggest that alveolar type II cells also have the potential to give rise not only to SCLC, but to EGFR-mutant adenocarcinoma as well.<sup>4</sup> It has since been postulated that the presence of EGFR mutation and constitutively active EGFR signalling drives the proliferation and differentiation of alveolar type II cells. The use of EGFR tyrosine kinase inhibitors blocks this effect, and when additional genetic events such as *RBI* inactivation occur, these same alveolar type II cells might subsequently transform to SCLC.<sup>4</sup>

The clinical course of patients with EGFR-mutant adenocarcinomas that underwent histologic transformation to SCLC is poorly characterized. In the 2019 study by Marcoux *et al.*, the median time to transformation was 17.8 months.<sup>8</sup> Treatment after transformation with platinum-

etoposide and taxanes yielded high response rates. The tumors were unresponsive to checkpoint inhibitors. Median overall survival since the time of SCLC transformation was 10.9 months.<sup>8</sup> Another study showed a median progression-free survival after SCLC transformation of only two months when treated with tyrosine kinase inhibitor monotherapy and six months when treated with etoposide combined with cisplatin or carboplatin.<sup>15</sup> In our case, the patient was only given one cycle of carboplatin and etoposide and expired soon after the diagnosis of SCLC was made.

In summary, we have presented a case of a 64-year old Filipino male with a known EGFR-mutant adenocarcinoma that was treated with Afatinib and subsequently developed resistance through phenotypic transformation to small cell carcinoma after 17 months of therapy. Targeted therapy has only recently become widely available in the Philippines and, to our knowledge, this is the first fully-documented case of histologic transformation occurring in a Filipino patient. As molecular targeted therapy and immunotherapy become standard-of-care in our country, it is of paramount importance that clinicians and pathologists are aware of the various mechanisms of resistance that can occur as a result of these treatments.

#### STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

#### AUTHOR DISCLOSURE

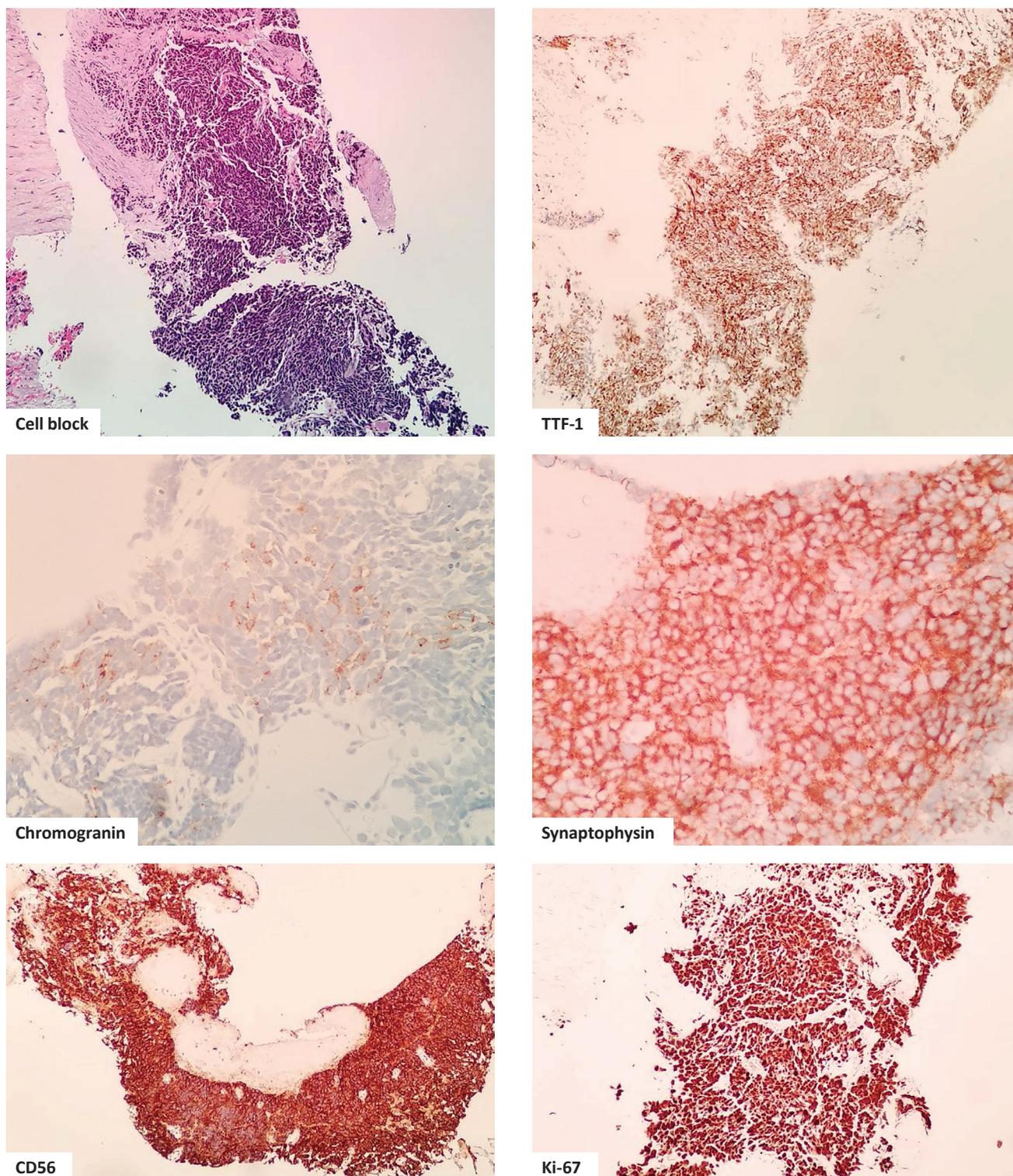
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**Supplemental Figure 1. Immunohistochemical studies done on the cell block.** The tumor was positive for TTF-1, chromogranin A, synaptophysin, and CD56. Ki-67 was high (more than 90%). All controls showed appropriate immunoreactivity. (H&E, TTF-1, CD56, and Ki-67 at 100X magnification; chromogranin and synaptophysin at 400X magnification).

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