

## Case Report

# Histological transformation of adenocarcinoma to small cell carcinoma lung as a rare mechanism of resistance to epidermal growth factor receptor-tyrosine kinase inhibitors: Report of a case with review of literature

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## ABSTRACT

A subset of non-small cell lung carcinoma (NSCC) harbor active mutations of epidermal growth factor receptor (EGFR). In these, EGFR tyrosine kinase inhibitors (EGFR-TKIs) are recommended as the first-line treatment. Though drug resistance is inevitable, histological transformation to small cell lung carcinoma (SCLC) is a rare mechanism for acquired resistance. Here we report one such rare case of histological transformation of pulmonary adenocarcinoma to small cell lung carcinoma in 46 year old male treated with Gefitinib.

**KEY WORDS:** Acquired resistance, epidermal growth factor receptor, histological transformation, nonsmall cell lung carcinoma, small cell lung carcinoma, tyrosine kinase inhibitor

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## INTRODUCTION

The nonsmall cell lung carcinoma (NSCC) harbors active mutations of epidermal growth factor receptor (EGFR). Majority of the EGFR mutations are located in tyrosine kinase binding domain (exon 18–21). The exon 19 deletion and exon 21 L858R point mutation encompasses almost 90% of the active mutations.<sup>[1]</sup> Current treatment guidelines recommends EGFR tyrosine kinase inhibitors (EGFR-TKIs) as the first-line treatment for a subset of EGFR-mutated NSCC.<sup>[2]</sup> In spite of a high rate of therapeutic response to EGFR-TKIs, drug resistance is inevitable and occurs on an average within a year.<sup>[3]</sup> Acquired resistance occurs through emergence of a secondary mutation of T790M and activation of bypass signal transduction pathway. Histological

transformation to small cell lung carcinoma (SCLC) is a rare mechanism.<sup>[1]</sup> Here, we report one such rare case. A comprehensive literature search has shown very few cases mostly in the form of case reports documented in the recent years. The largest series has been reported from Korea comprising of six cases.<sup>[4]</sup> To the best of our knowledge, such histological transformation has not been described in Indian literature till date.

## CASE REPORT

A 46-year-old male, a known smoker presented with backache for 1 month. There was no loss of sensation

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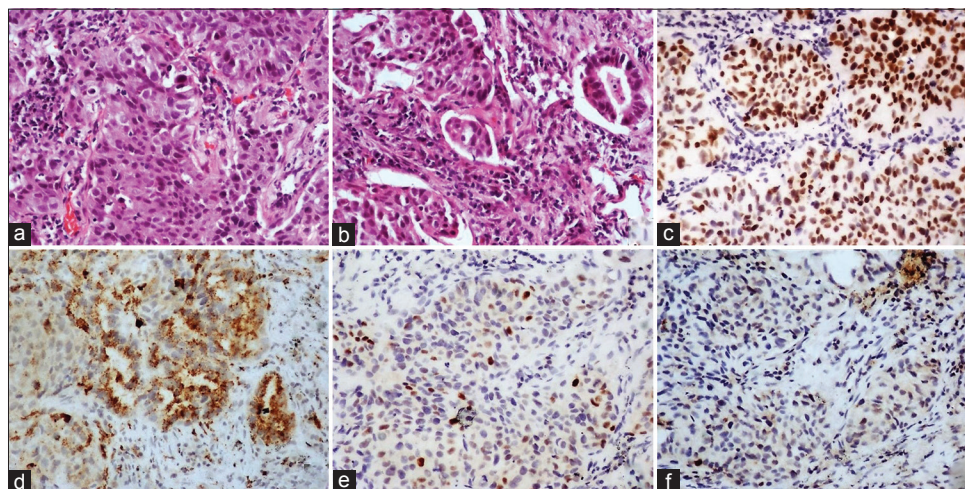
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or weakness of the lower limbs. There was no history of cough shortness of breath, chest pain, headache, vomiting, and seizures. He was evaluated at an outside hospital. Magnetic resonance imaging of spine showed altered signal intensities which were hypointense on T1 and hyperintense on T2/STIR in the body, pedicle and lamina of L5, and D9 vertebral bodies and bilateral iliac bones suggestive of metastasis. On further workup, whole body fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) scan showed increased uptake in large lobulated mass lesion with surrounding spiculations in the posterior segment of the right upper lobe, abutting major fissure. There was nodular pleural thickening on the right side with minimal loculated pleural effusion. On examination, basal crepts were heard on the right side. Laboratory parameters were within normal limits. Core biopsy of the lung was done. Histopathology was suggestive of adenocarcinoma (ADC) showing predominantly solid pattern with focal acinar formation [Figure 1a and b]. Immunohistochemistry (IHC) showed diffuse positivity for ADC markers thyroid transcription factor 1 (TTF1) and napsin A. Among the squamous cell markers, P63 stained some of tumor cell nuclei while p40 was negative [Figure 1c-f]. A diagnosis of pulmonary ADC was thus confirmed on IHC. He was started on chemotherapy with pemetrexed, carboplatin and zoledronate. Subsequently, EGFR analysis done on formalin fixed paraffin-embedded tissue block revealed exon 19 mutation. After completion of 4 cycles of chemotherapy, he was started on switch maintenance with gefitinib and was continued for a period of 1 year. On follow-up, PET CT was done to assess the disease response. Compared to the previous PET CT, there was an increase in size and FDG uptake of primary right lung lesion, pleural deposit, and effusion. He also developed ill-defined enhancing lesions in bilateral frontal lobes and left cerebellum. On examination, there was multiple level

IV lymph nodes in the right cervical region. The breath sounds were reduced on the right side. There were no focal neurological deficits. In view of progressive disease, a repeat biopsy of the right pleural-based lesion was done. Biopsy revealed round to polygonal cells in sheets, nests, and trabeculae. The cells had scant cytoplasm, high N: C ratio, and hyperchromatic nuclei with molding and spindling [Figure 2]. On IHC, the cells showed diffuse strong positivity for TTF1, chromogranin and synaptophysin. Ki-67 showed increased labeling (>90%) in tumor cells [Figure 3a-d]. Napsin A and p40 were distinctly negative while p63 showed weak nuclear staining in some tumor cells [Figure 3e-g]. Biopsy features this time were thus suggestive of small cell carcinoma. There was no evidence of ADC component in this biopsy. In view of histological transformation from nonsmall cell to small cell carcinoma, the previous biopsy was again reviewed. It did not show any evidence of small cell component. Repeat EGFR analysis on this second biopsy also revealed exon 19 deletion similar to the initial biopsy ruling out a second de novo primary. The tumor was negative for T790M mutation. He was started on chemotherapy with 6 cycles of carboplatin and etoposide for small cell component and cranial radiotherapy for brain metastasis. Gefitinib was discontinued. At 3 months follow up, he showed symptomatic improvement.

## DISCUSSION

There are various mechanisms of acquired resistance to EGFR inhibitors. Acquired resistance arising from T790M mutations and bypass of EGFR signaling through MET and HER2 amplification accounts for 50%–60% and 15%–20% of resistant cases, respectively.<sup>[5-7]</sup> The former increases the affinity of EGFR receptor for ATP leading to continued EGFR signaling even in the presence of the inhibitor.<sup>[8]</sup> Histological transformation of NSCC to



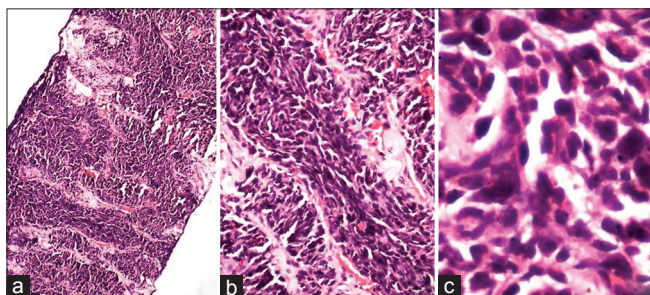
**Figure 1:** (a and b) Section show infiltrating lesion comprised of polygonal cells arranged is predominantly in solid nests and islands with focal acinar (black arrow) pattern (H and E;  $\times 100$ ). (c) Thyroid transcription factor-1 showing diffuse strong nuclear positivity in tumor cells (Poly-HRP;  $\times 100$ ). (d) Napsin A showing granular cytoplasmic positivity in tumor cells (Poly-HRP;  $\times 100$ ). (e) P63 showing positivity in nuclei of some tumor cells (Poly-HRP;  $\times 100$ ) and (f) p40 negative in tumor cells (Poly-HRP;  $\times 100$ )

SCLC has been recently described as a rare mechanism of acquired resistance accounting for 3% of cases.<sup>[6]</sup> It was first described in 2006 in a 45-year-old woman with EGFR-mutant ADC following treatment with erlotinib.<sup>[9]</sup> The absence of T790M mutation in the repeat biopsy following treatment with EGFR-TKI points toward histological transformation responsible for acquired resistance in this case. Although the exact mechanism is not clear, it can be possibly attributed to the alteration of morphology from NSCC, mostly ADC, to high-grade neuroendocrine phenotype (SCLC).<sup>[10]</sup> The combined small cell carcinomas which may not be apparent on the initial diagnostic biopsy can also lead to sampling errors, especially in small biopsies. In such cases, sampling of different histological areas in the initial and repeat biopsy may be misleading. The SCLC component may persist and dominate the histology following successful treatment of the ADC component by EGFR inhibitor. Thus, genomic sequencing of EGFR mutation in original tumor and transformed SCLC at the time of resistance helps in

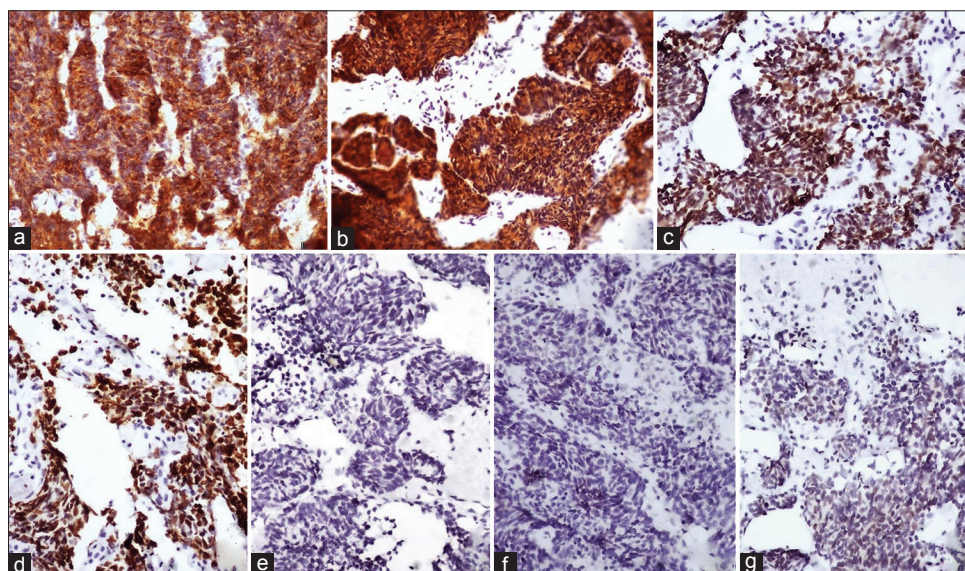
resolving such issues.<sup>[4]</sup> Similar to other reported cases, the repeat biopsy following treatment retained the original EGFR-activating mutation in the present case ruling out an independent second primary malignancy.<sup>[5]</sup> Ahn *et al.* in their series of six cases of ADC reported histologic transformation to SCLC following TKI therapy in four cases which had EGFR activating mutations.<sup>[4]</sup> Jiang *et al.* in his meta-analysis of 18 cases noted EGFR mutations in 16 cases of which 61% had exon 19 deletion and 28% had exon 21 point mutation. Among these, 11 SCLC retained the same mutation as their ADC counterparts.<sup>[11]</sup>

The possibility of histological transformation to SCLC should be suspected in cases with clinical and radiological progression of disease following treatment with TKIs. A repeat biopsy should be performed in all such cases to confirm progression to SCLC. The current case showed radiological evidence of increase in size and uptake of the original lesion as well as new lesion in the brain when compared with the initial radiological findings at diagnosis. It is important to identify small cell component on histology in view of good therapeutic response to targeted SCLC chemotherapy regimen.<sup>[12]</sup>

Furthermore, Norkowski *et al.* reported small cell transformation in EGFR-mutant tumors before treatment with TKIs. This suggests that EGFR inhibition is not solely responsible for phenotypic change in EGFR-mutant cases.<sup>[13]</sup> Similar histological transformation has also been reported in cases of acquired resistance to crizotinib in anaplastic lymphoma kinase rearranged lung tumors.<sup>[14]</sup> Large cell neuroendocrine carcinoma transformation has also been described in literature as an acquired resistance mechanism to EGFR TKIs and as well as crizotinib.<sup>[15,16]</sup>



**Figure 2:** (a-c) Section show infiltrating lesion comprised of sheets and trabeculae of polygonal cells. These cells have high N:C ratio with scant cytoplasm. Nuclei show evidence moulding and spindling with inconspicuous nucleoli (H and E; [a]  $\times 40$ , [b]  $\times 100$ , [c]  $\times 400$ )



**Figure 3:** Immunohistochemistry findings. (a) Chromogranin and (b) synaptophysin showing diffuse strong cytoplasmic positivity in tumor cells (Poly-HRP;  $\times 100$ ). (c) Thyroid transcription factor-1 showing diffuse nuclear positivity in tumor cells (Poly-HRP;  $\times 100$ ). (d) Ki-67 highlighting very high proliferative activity in tumor cells (Poly-HRP;  $\times 100$ ). (e) Napsin A and (f) p40 negative in tumor cells (Poly-HRP;  $\times 100$ ). (g) P63 showing weak nuclear staining in some of the tumor cells (Poly-HRP;  $\times 100$ )

## CONCLUSION

This case highlights the importance of additional biopsy in all cases of progressive disease following treatment with EGFR-TKIs to rule out possibility of an acquired resistance. Identification of histologic transformation to small cell component is important as therapy can be switched to etoposide and cisplatin against SCLC.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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