Case Report

Unravelling the complexity of *EGFR*-mutated lung adenocarcinoma: a unique case report with histological transformations and co-alteration acquisition

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Background: Osimertinib, a third-generation tyrosine kinase inhibitor that targets epidermal growth factor receptor (EGFR), specifically inhibits both EGFR tyrosine kinase inhibitor-sensitive mutations and T790M resistance mutations. Despite initial positive responses to EGFR tyrosine kinase inhibitors, nearly all patients eventually experience disease progression. Mechanisms of resistance are classically divided into EGFR-dependent and EGFR-independent mechanisms, such as the activation of alternative pathways and histological changes. We report a case of histological transformation into large cell carcinoma associated with the subsequent acquisition of an anaplastic lymphoma kinase (ALK) rearrangement after osimertinib exposure.

Case Description: A 67-year-old female with no smoking history presented with supraclavicular lymphadenopathy and asthenia, which led to a diagnosis of stage IVB lung adenocarcinoma. Next generation sequencing (NGS) identified an *EGFR* Ex19del mutation, which suggested the use of afatinib, as it was prescribed prior to osimertinib and was covered by insurance. Initial treatment with afatinib resulted in partial remission, followed by pulmonary progression without the *EGFR*-T790M mutation. Moreover, ALK and ROS1 were identified through immunohistochemistry (IHC), with ROS1 expression subsequently confirmed by fluorescence in situ hybridization (FISH); this prompted a switch to crizotinib, which was discontinued owing to further disease progression. Osimertinib was then administered, which resulted in a significant positive response; however, after six months pulmonary progression was observed. A subsequent biopsy indicated a transformation to large cell neuroendocrine carcinoma, which led to treatment with platinum-etoposide chemotherapy and, later, paclitaxel and osimertinib, both of which are partially effective. Finally, a new biopsy confirmed ALK positivity in a large cell neuroendocrine carcinoma that was still harbouring an *EGFR* exon 19 deletion, so alectinib was introduced.

Conclusions: To our knowledge, this case is the first reported incidence of transformation into large cell carcinoma coupled with a second acquisition of alterations in ALK. These findings underscore the necessity of monitoring patients with oncogenic addiction through both liquid biopsy for on-target mechanism detection and tissue sampling to detect histological transformations. These mechanisms can occasionally be

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combined, thereby providing comprehensive panels at each stage of tumour progression.

Keywords: Epidermal growth factor receptor (EGFR); large-cell neuroendocrine carcinoma (LCNEC); transformation; anaplastic lymphoma kinase (ALK); case report

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Introduction

Background

Epidermal growth factor receptor (EGFR) inhibitors have transformed the management of *EGFR*-mutated (EGFRm) non-small cell lung carcinoma (NSCLC). However, relapse occurs in all patients, typically within 8–17 months of starting EGFR-tyrosine kinase inhibitor (TKI) therapy (1). The resistance mechanism observed is the *EGFR* T790M mutation in exon 20, which is identified in approximately 60% of patients resistant to treatment (2,3).

Rationale and knowledge gap

Osimertinib, a third-generation EGFR-TKI, irreversibly inhibits *EGFR*-activating mutations (e.g., exon 19 deletion or L858R) and the T790M mutation. In the FLAURA trial, osimertinib was superior to other EGFR-TKIs in untreated, advanced EGFRm NSCLC patients, with a median progression-free survival (PFS) of 18.9 months (1). However, similar to first- and second-generation EGFR-TKIs, resistance to osimertinib is inevitable. Various resistance mechanisms have been identified, including the rare occurrence of transformation to small cell lung cancer (SCLC) in approximately 2% of patients (4). Large-cell lung cancer neuroendocrine carcinoma (LCNEC) transformation remains exceptional.

Objective

Hence, we report a unique documented case of a histological transformation into large cell carcinoma of an *EGFR* exon 19-mutated lung adenocarcinoma after osimertinib, followed by an anaplastic lymphoma kinase (ALK) alteration. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-707/rc).

Highlight box

Key findings
- Anaplastic lymphoma kinase (ALK) rearrangement can occur even after histological transformation into large cell carcinoma in the context of epidermal growth factor receptor (EGFR)-mutated non-small cell lung carcinoma (NSCLC) under osimertinib treatment.

What is known and what is new?
- Liquid biopsy is useful for the management of NSCLC patients harbouring actionable genetic alterations, but it is potentially insufficient for exploring histological transformation resistance mechanisms under targeted therapy.
- This unique case report documents a histological transformation into large cell carcinoma of an EGFR exon 19-mutated lung adenocarcinoma, followed by an ALK rearrangement acquisition.

What is the implication, and what should change now?
- This illustrates the need for rebiopsying even after the discovery of an off-target mutation to conduct systematic molecular analyses, including other signalling pathways beyond the primary molecular alteration.

Case presentation

A 67-year-old female with no history of smoking or significant medical conditions presented with supraclavicular lymphadenopathy and asthenia. A biopsy of the lymphadenopathy revealed lung adenocarcinoma characterized by positive staining for cytokeratins 7 (CK7) and thyroid transcription factor-1 (TTF-1) (*Figure 1A-1D*). Staging at the time of diagnosis indicated stage IVb (American Joint Committee on Cancer 7th edition) disease with a T4 primary tumour, extensive regional lymph node involvement (N3), and distant metastases (M1c), including multiple bilateral pulmonary nodules, metastatic bilateral hilar lymph nodes, bilateral pleural effusion, a right adrenal lesion, and several secondary bone and brain metastases.

Immunohistochemical staining showed ALK negativity.

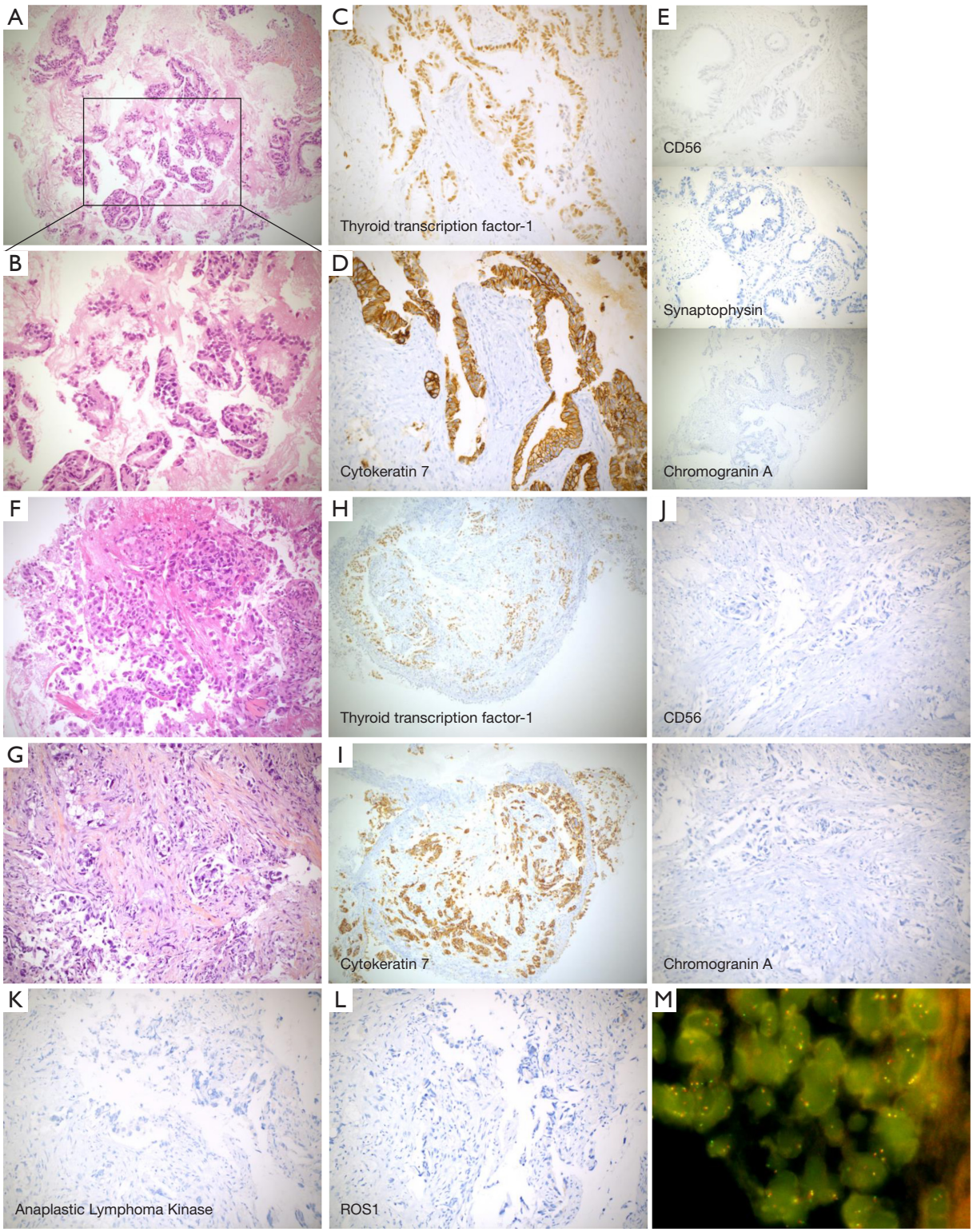

Figure 1 Biopsies revealed a metastatic lung adenocarcinoma, supported by immunohistochemical markers. The tumor was positive for TTF-1 and CK7, negative for neuroendocrine markers, and showed no ALK or ROS1 rearrangements by IHC, though ROS1 was positive by FISH. Biopsy of a supraclavicular lymph node showing metastatic tumour proliferation with a tubulo-glandular architecture, composed of

cylindrical cells with clear, mucin-secreting cytoplasm (A, HE, ×100). The nuclei exhibit marked cytonuclear atypia, including anisokaryosis and hyperchromasia (B, HE, ×200). The tumour was positive for TTF-1 (C, IHC, ×200) and CK7 (D, IHC, ×200). It was negative for neuroendocrine markers (E, IHC, ×200), including CD56, synaptophysin, and chromogranin A (top to bottom). Bronchial biopsy of the primary tumour revealed that the tumour cells were arranged either as isolated cells or in three-dimensional structures (F, HE, ×200), with a markedly increased nuclear-cytoplasmic ratio. The nuclei were vesicular with prominent nucleoli. These cells focally infiltrated the bronchial wall within a reactive fibroinflammatory stroma (G, HE, ×200). The tumour was positive for TTF-1 (H, IHC, ×100) and CK7 (I, IHC, ×50) but negative for neuroendocrine markers (J, IHC, ×200), including CD56 and chromogranin A (top to bottom). ALK (K, IHC, ×200) and ROS1 (L, IHC, ×200) staining by IHC was negative, whereas ROS1 was positive by FISH analysis (M) (×400). IHC was performed with anti-ALK clone 1A4 (Diagomics) and anti-ROS1 clone D4D6 (Ozyme) antibodies on a Ventana instrument (Roche Diagnostics). Positive staining corresponded to the presence of a cytoplasmic signal for more than 10% of the tumour cells. FISH analysis was performed with the ZytoLight SPEC Dual Colour Break Apart Kit (Zytovision) for ALK and ROS1, with the split orange signals indicated by red arrowheads; a nucleus was interpreted as positive for translocation if the split orange and green signals were separated by more than two signal diameters. ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; HE, hematoxylin and eosin; TTF-1, thyroid transcription factor-1.

ROS1 chromosomal rearrangements were detected by fluorescence *in situ* hybridization (FISH) in 46% of the tumour cells, whereas ALK rearrangements were less significant and were found in only 6% of the tumour cells (*Figure 1*). The first DNA next generation sequencing (NGS) test, performed in March 2017 via the Tumour Hotspot MASTR Plus assay (Multiplicom, Niel, Belgium), targeted 252 amplicons (121–254 bp) from 26 relevant cancer genes. The sequencing data were analysed using the Sophia Genetics DDM platform (Rolle, Switzerland). The analysis revealed a molecular alteration in EGFR (E746_750 deletion located in exon 19) which led to the initiation of afatinib treatment, in accordance with the guidelines and indications available in 2017 predating the approval of osimertinib for first-line therapy. An *EGFR* exon 19 deletion was detected at an allelic frequency of 94%, with a coverage of 18,221×, which was significantly greater than that of other covered regions, suggesting the presence of amplification along with exon 19 deletion in the *EGFR* gene. No cooccurring alterations were identified in the other genes tested, including tumor protein 53 (TP53) and retinoblastoma protein 1 (RB1), which were not targeted by this assay. An initial tumour response was observed, as well as a decrease in the copy number of the *EGFR* exon 19 mutation in circulating tumor DNA (ctDNA). However, at the 15-month mark, pulmonary progression occurred without the presence of an *EGFR* T790M gatekeeper mutation. As a second-line treatment, crizotinib was initiated but had to be discontinued after 2 months because of significant and widespread progression, including pleural involvement.

Molecular analyses of the pleural effusion confirmed the presence of the *EGFR* exon 19 deletion and, notably, revealed the emergence of an *EGFR* T790M mutation in exon 20, with no evidence of ALK or ROS1 rearrangements. This second NGS analysis was performed in August 2018 with the Tumour Hotspot MASTR Plus assay. The *EGFR* exon 19 deletion was detected at a frequency of 84%, with a coverage of 21,067× *EGFR* T790M mutation and an allelic frequency of 15%, with a coverage of 3,342×. Osimertinib was subsequently administered, which resulted in substantial clinical and radiographic responses.

Pulmonary progression was evident six months after treatment initiation. Subsequent endobronchial biopsies confirmed the presence of tumour cells with positive staining for CK7 and TTF-1, whereas programmed death-ligand 1 (PD-L1) staining was negative. The morphological assessment raised doubts about the possibility of a SCLC diagnosis, primarily due to the limited tissue sample obtained during the biopsy. Additionally, results for synaptophysin, chromogranin A, and cluster of differentiation 56 (CD56) immunostaining results were negative. As a result, a percutaneous computed tomography (CT)-guided lung biopsy was performed, which revealed the presence of a large cell neuroendocrine carcinoma with a Ki67 index of 80%. Immunohistochemical staining demonstrated positivity for synaptophysin, CD56, and chromogranin A, with negative results for TTF-1, PD-L1, and p40 (*Figure 2*). The third NGS evaluation (December 2019) was performed with the large FoundationOne Cdx gene panel (Foundation Medicine, Inc., San Diego, CA, USA), which targeted 324 genes and allowed for the detection of single-nucleotide variants (SNVs), indels, copy number variations (CNVs), selected clinically relevant

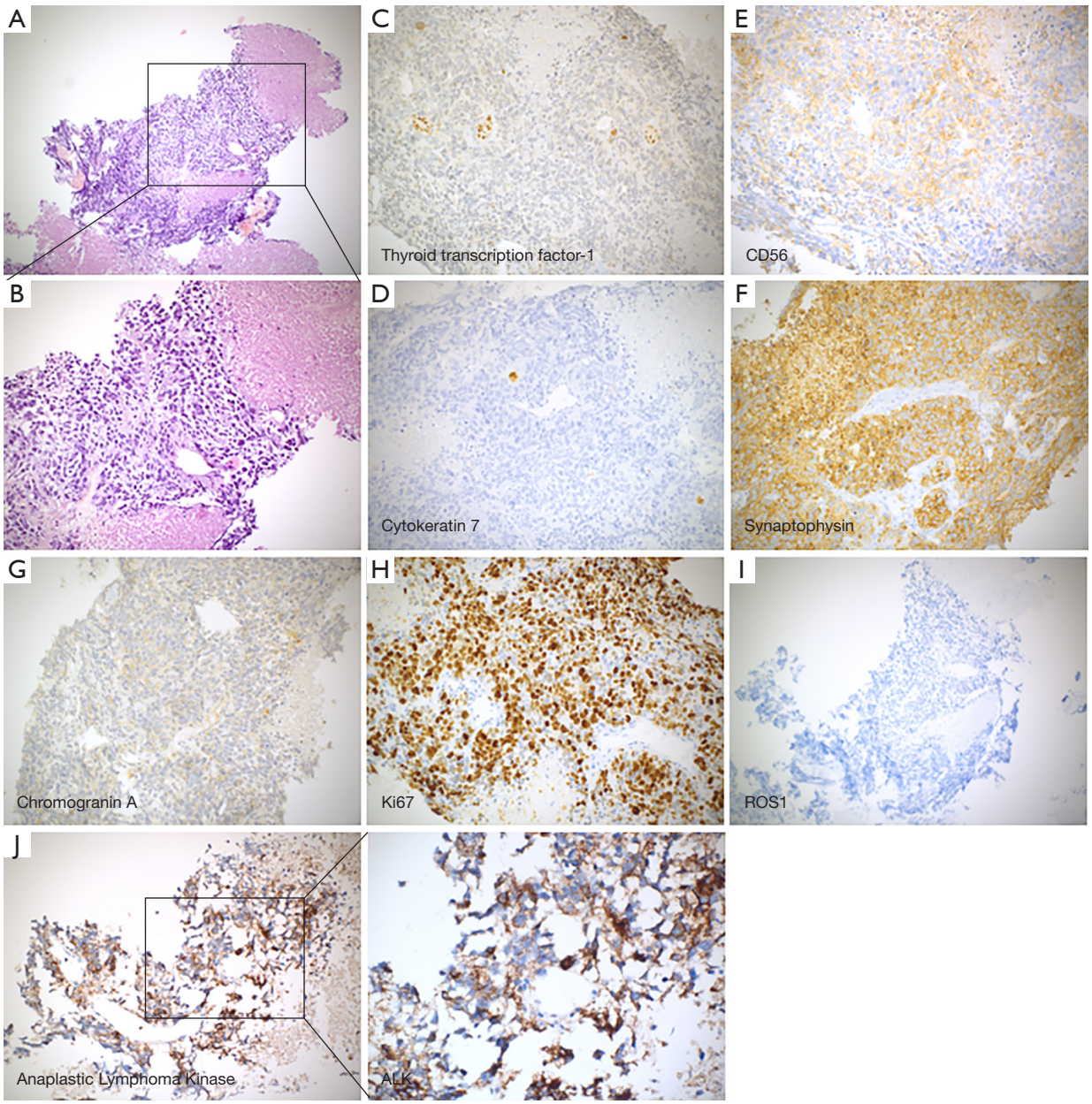

Figure 2 Further biopsies revealed transformation into large-cell neuroendocrine carcinoma as suggested by loss of TTF-1 and CK7 expression, positivity for neuroendocrine markers CD56, synaptophysin, chromogranin A) and a high proliferative index with Ki67 >80%. This histologic transformation was accompanied by the acquisition of an ALK translocation, as evidenced by a 3+ staining pattern for ALK, with persistent absence of ROS1 expression. HE staining showed bronchial parenchyma infiltrated by poorly differentiated proliferating tumours with a carcinomatous architecture composed of confluent sheets of large cells (A, HE, ×50). These cells had hyperchromatic nuclei, sometimes with irregular contours and prominent nucleoli, which displayed a fine salt-and-pepper chromatin pattern. The cytoplasm was eosinophilic, sparse, and had well-defined borders (B, HE, ×100). The tumour cell sheets were separated by extensive areas of necrosis. The tumour cells were negative for TTF-1 (C, IHC, ×200) and CK7 (D, IHC, ×200) staining. Tumour cells were positive for neuroendocrine markers, including CD56 (moderate staining, E, IHC, ×200), synaptophysin (intense staining, F, IHC, ×200), and chromogranin A (moderate staining, G, IHC, ×200). More than 80% of the tumour cells were positive for Ki67 (H, IHC, ×200). ROS1 staining remained negative by IHC (I, IHC, ×100), while ALK staining was positive by IHC, with a score of 3+ (J, IHC, ×100 on the left, ×200 on the right). ALK, anaplastic lymphoma kinase; HE, haematoxylin and eosin; IHC, immunohistochemistry; TTF-1, thyroid transcription factor-1.

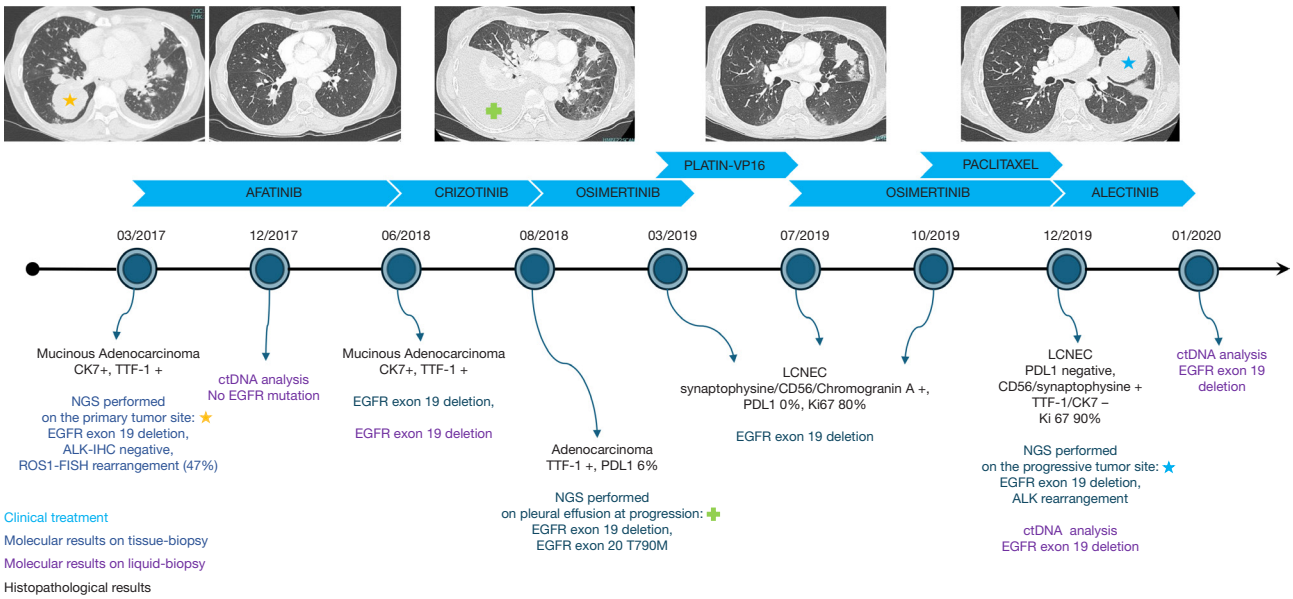

Figure 3 Evolution of the tumour response over time in response to various therapies. This figure illustrates the temporal evolution of the tumour response categorized by different therapeutic interventions, accompanied by histopathological evaluations and molecular biology findings from tissue samples and/or liquid biopsies. Molecular results have been differentiated between those obtained from tissue analyses and those from ctDNA. Icons placed alongside the NGS analyses indicate the source of the sample analyzed. The detection of *EGFR* mutations in cell-free DNA was performed with the TaqMan PrimePCR™ ddPCR mutation assay (Bio-Rad) via digital PCR on a QX200 AutoDG droplet digital system (Bio-Rad). NGS, next generation sequencing; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; ctDNA, circulating tumor DNA; PDL1, programmed death-ligand 1; LCNEC, large-cell lung cancer neuroendocrine carcinoma; PCR, polymerase chain reaction; TTF-1, thyroid transcription factor-1.

gene rearrangements, tumour microsatellite instability, and tumour mutational burden. This analysis detected an *RB1* mutation (splice site 1421+2T>G, classified as likely oncogenic, likely loss of function), along with a *TP53* mutation (D281H, classified as likely oncogenic, likely loss of function). The FoundationOne Cdx report did not note allelic frequencies at that time (this information became available later in F1 reports). Notably, RNA NGS reaffirmed the persistence of the *EGFR* exon 19 deletion and the absence of chromosomal rearrangements for ALK/ROS1 or the *EGFR* T790M mutation. The continued presence of the *EGFR* oncogenic mutation within a different histological subtype reasonably suggested the occurrence of a histological transformation.

The treatment regimen was subsequently switched to fourth-line chemotherapy using a cisplatin and etoposide regimen, during which three cycles were administered, which resulted in a partial tumour response. This was followed by three additional cycles, during which cisplatin was replaced with carboplatin due to cisplatin-induced ototoxicity. Osimertinib was continued until cycle 2 and day 1. Partial responses observed after six cycles of induction prompted an empirical maintenance strategy involving osimertinib on the basis of the continued detection of the *EGFR* exon 19 mutation in circulating cell-free DNA.

However, cerebral and pulmonary progression occurred at 3 months, which led to the initiation of a new chemotherapy regimen that included a combination of paclitaxel and osimertinib, which unfortunately proved ineffective.

Finally, a new CT-guided lung biopsy confirmed the presence of a large cell neuroendocrine carcinoma of the lung, the persistence of the *EGFR* exon 19 deletion, and the absence of the *EGFR* T790M mutation. Notably, ALK immunostaining yielded a strong positive result (3+), which was further confirmed by FISH (rearrangement present in 25.2% of tumour cells), whereas the ROS1 tests remained negative. Alectinib was subsequently introduced. Unfortunately, no further reevaluation was possible due to the sudden death of the patient in her home. The clinical management is summarized in *Figure 3*.

Ethical statement

Access to patient data for this retrospective report was approved by the French National Commission for Personal Data Protection (CNIL, Comité National de l'Information et des Libertés) under registration number MR004020820243. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Publication of this case report and accompanying images was waived from patient consent according to the local ethics committee and institutional review board.

Discussion

While significant progress has been made in understanding *EGFR* mutations, challenges persist. *EGFR* is considered an actionable oncogenic alteration (AGA) in NSCLC, alongside other targetable alterations, such as *ALK*, *ROS1* rearrangements, *BRAF*, *ERBB2* and *KRAS* (V-Ki-ras2 Kirsten rat sarcoma) G12C mutations (5). Activating mutations in the *EGFR* gene account for 10–35% of lung adenocarcinomas, with L858R exon 21 mutations and exon 19 deletions being the most common, occurring in 80–90% of cases. Uncommon alterations, such as exon 20 insertions and G719X, L861Q, and S768I mutations, are found in approximately 10% of *EGFR*-mutated tumours (6). The FLAURA study established osimertinib as the standard first-line treatment for advanced NSCLC patients harbouring *EGFR* mutations, with a median PFS (mPFS) and overall survival times of 18.9 and 38.6 months, respectively (1). While AGAs such as *EGFR*, *KRAS*, and *ALK* are generally considered mutually exclusive, some studies have reported their co-occurrence. There are an increasing number of publications reporting coalterations identified through new molecular techniques with enhanced sensitivity and expanded panels, particularly in DNA sequencing and, more notably, in RNA sequencing for fusion transcripts (7). The percentage of EGFR-ALK coalterations reported in the literature, alongside EGFR, is estimated to be between 4% and 15% of ALK-translocated cases, depending on the technique used (8). In NSCLC, *EGFR* is the gene most commonly associated with coalterations, including *ALK*, and is linked to a reduced PFS (9). For example, Guibert *et al.* reported that only 165 patients (0.93%) exhibited multiple genetic alterations involving oncogenic drivers. Specifically, 0.91% had double mutations, and 0.02% had triple mutations (10). The most frequent comutations emerging *de novo* with *EGFR* were *PIK3CA*, *KRAS*, *ALK* (n=10), and *BRAF* mutations. Conversely, a study by Gainor *et al.* analysed 1,683 NSCLC tumours and reported no comutations (11). Other coalterations, such as those in EGFR-ROS1, have also been described (10). In cases of comutation, determining the best treatment is challenging (12). Shin *et al.* published a case series describing three patients diagnosed with advanced nonsquamous NSCLC who presented with coalterations of EGFR and ALK (13). All three patients received first-line therapy with EGFR-TKIs. In two of the patients, ALK-TKIs were given as a second-line therapy, followed by additional EGFR-TKIs in subsequent lines. While all patients demonstrated partial responses to EGFR-TKIs, second-line ALK-TKI therapy was ineffective in two of the patients. Liu *et al.* published a study involving a larger cohort of 419 patients with ALK-rearranged NSCLC to investigate coalterations in the EGFR kinase domain (14). The overall frequency of concomitant EGFR and ALK alterations was 5.01% (21/419). Notably, the rate of EGFR alterations in patients with EML4-ALK coalterations was significantly lower (3.06%, 11/359) than that in patients with non-EML4-ALK alterations (16.67%, 10/60; P<0.01). Among patients previously treated with EGFR-TKIs (n=16), Kaplan-Meier analysis revealed that those with EML4-ALK/EGFR coalterations (n=7) had a significantly shorter PFS after EGFR-TKI treatment than non-EML4-ALK/EGFR coaltered patients did (n=8; mPFS: 6.0 *vs.* 15.0 months, P=0.046). Among the five patients whose EGFR/ALK coaltered genes were treated with single TKIs, the outcomes varied, whereas three patients receiving dual-TKI treatment (EGFR-TKI plus ALK-TKI) achieved a PFS greater than 5 months (8.4, 8.6, and >5.2 months). These findings suggest distinct clinical features and responses to EGFR-TKIs between EML4-ALK/EGFR and non-EML4-ALK/EGFR coalterations, with the latter potentially representing a resistance mechanism to EGFR-TKIs. Additionally, dual-TKI therapy may be more effective than single-TKI treatments for these coaltered patients. The allelic fraction of each alteration provided by NGS can help determine the predominant clone to target. Additionally, NGS, especially for RNA transcripts, is essential for eliminating false-positives (7).

Various techniques, including FISH, immunohistochemistry (IHC), and molecular methods such as NGS, are used to detect ALK/ROS1 rearrangements. In routine practice, FISH +/– IHC is the reference standard, but false-

positives can occur, necessitating the use of RNA NGS to confirm results. Additionally, RNA NGS allows for the characterization of ALK fusion variants (specifically EML4/ALK variants v1, v2, and v3), which can impact the response to TKIs (15,16). For ALK detection, RNA NGS has shown superior sensitivity (83.33%) compared with that of IHC (33.33%). Similarly, RNA NGS is considered the gold standard for confirming ROS1-positive NSCLCs identified via IHC, with 100% specificity (17).

In our case, the emergence of the ALK fusion may have represented a mechanism of resistance to EGFR TKIs. This phenomenon has been observed in clinical trials, with 3–10% of patients developing oncogenic fusions involving the RET/BRAF/ROS1 or ALK genes after exposure to osimertinib (18). The detection of ROS1 rearrangements led to the introduction of crizotinib as a second-line treatment, but subsequent molecular analyses did not confirm the presence of this rearrangement, which suggested a false-positive result from ROS1 detection by IHC (19). In cases of coalterations involving driver genes, the clinical guidelines in the literature remain unclear, especially given the limited number of cases. Therefore, further studies are needed to understand the responses and resistance to EGFR-TKIs and ALK-TKIs. An absence of benefit from ALK TKI treatment could also be suspected, given that *EGFR* mutations have been described as mechanisms of resistance to ALK inhibitors (20).

Previous case reports have documented rare instances of LCNEC with ALK alterations, along with the efficacy of treatments targeting ALK (21-23). Our case does not allow for the evaluation of the benefit of ALK-targeted therapy due to the early and unexplained death of our patient. However, it can be hypothesized that the combination of histological transformation with a second molecular driver (i.e., EGFR) could contribute to a poorer response to targeted therapies.

We could also hypothesize that a clonal evolution of the *EGFR* mutation (present in nearly all tumour cells) and a selection pressure potentially favouring either a large-cell neuroendocrine component and/or a subclonal alteration of ALK rearranged tumour cells (24). However, consecutive liquid biopsies did not provide any evidence to support this hypothesis. The literature indicates that oncogenic drivers, such as EGFR, typically undergo clonal evolution in a nearly systematic manner (25). We considered the hypothesis of a composite pulmonary carcinoma with both adenocarcinomatous and large cell components. However, the concordance between the two biopsy sites in identifying only the adenocarcinomatous component, along with the consistent negativity for neuroendocrine markers, does not support this theory. The transformation to large-cell neuroendocrine carcinoma, concurrent with the emergence of a strongly positive (3+) ALK rearrangement, could also lead to the question of the specificity of molecular analysis. Some authors previously reported that IHC is not a reliable diagnostic tool for detecting ALK rearrangement in pulmonary neuroendocrine tumours, given its low specificity and high frequency of false-positive results (26). Similar findings have been reported in other tumour types, such as neuroblastomas, where MYCN amplification has been associated with false-positive ALK expression (27). In contrast, in NSCLC, ALK positivity detected by IHC is considered diagnostic to support the use of ALK TKIs (5), although false-positive and discordant cases with FISH and NGS have also been reported, possibly due to ALK amplifications or activating mutations (28,29).

This case also underscores the clinical importance of liquid biopsy in the context of an oncogenic driver, despite its limitations. Liquid biopsy offers the advantage of assessing the entirety of a tumour's heterogeneity, uncovering resistance mechanisms such as on-target EGFR alterations. Importantly, liquid biopsy has limitations, as our case illustrates the potential for missing histologic transformations and additional undetected alterations, such as molecular rearrangements. This is particularly true for targeted approaches such as digital polymerase chain reaction (PCR). However, liquid biopsy NGS panels could address some of these limitations, particularly by detecting circulating fusions (30).

Finally, a personalized clinical management approach incorporating repeated molecular analyses and sequential liquid and tissue biopsies extended the overall survival of this patient. In the literature, only eight cases of large cell neuroendocrine carcinoma transformation have been reported (31). In all patients, the *EGFR* exon 19 deletion persisted, supporting the hypothesis that histologic transformation is associated with tumour resistance.

Conclusions

To our knowledge, this is the first case to combine an atypical histologic transformation after EGFR-TKI treatment with the acquisition of additional molecular alterations in subsequent AGA. This case highlights the importance of both liquid and tissue rebiopsies during disease progression, especially in the context of AGA. It also

underscores the need to identify histologic transformations, which may be missed by liquid biopsy, and to not automatically exclude the possibility of a subsequent AGA.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-707/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Access to patient data for this retrospective report was approved by the French National Commission for Personal Data Protection (CNIL, Comité National de l'Information et des Libertés) under registration number MR004020820243. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Publication of this case report and accompanying images was waived from patient consent according to the local ethics committee and institutional review board.

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