



# A case report of *EGFR* L861Q mutation in synchronous *de novo* small cell and non-small cell lung cancer: molecular interrogation identifies origin and potential options for targeted therapy

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**Background:** Lung cancer remains the leading cause of cancer death in the United States. Non-small cell lung cancer (NSCLC) comprises 85% of cases and small cell lung cancer (SCLC) comprises most of the remainder. Molecular profiling has drastically changed the landscape in regard to treating lung cancer and has become standard practice in management. Mutations in epidermal growth factor receptor (*EGFR*) are well studied and can be targeted using tyrosine kinase inhibitors providing new treatment opportunities for lung cancer. We present a unique case of synchronous malignancies with a possible common origin from a molecular perspective.

**Case Description:** We present a case of a 78-year-old female former smoker who presented after a screening mammogram detected bulky axillary lymphadenopathy and additional imaging found brain and bone lesions with two different sites biopsied identifying NSCLC and SCLC. Molecular profiling revealed a shared *EGFR* L861Q mutation which guided further in-depth molecular analysis. She was then treated with carboplatin AUC 4 and etoposide 65 mg/m<sup>2</sup> for two cycles after which she decompensated and expired before any further therapy could be offered. We discuss the common origin of the two malignancies, the benefit of *EGFR* directed therapy, and management of this particular patient given the molecular findings.

**Conclusions:** Molecular interrogation is a valuable tool to identify shared origin of synchronous malignancies. Given that our patient had a mutation that can be targeted which was harbored in both SCLC and NSCLC, treatment options included the addition of targeted treatment along with chemotherapy. The case presented provides a platform for academic discussion and highlights the importance of molecular tumor board discussions which can assist with guiding treatment.

**Keywords:** Non-small cell lung cancer (NSCLC); small cell lung cancer (SCLC); *EGFR* mutation; molecular profiling; case report

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## Introduction

Lung cancer remains the leading cause of cancer death in the United States. Non-small cell lung cancer (NSCLC) comprises 85% of cases and small cell lung cancer (SCLC) comprises most of the remainder (1). Targeted therapies have improved the prognosis of NSCLC; therefore, accurate determination of the genetic basis of lung cancer is essential for optimal management. Epidermal growth factor receptor (*EGFR*) mutations have been found in 26% of patients diagnosed with NSCLC (2) whereas *EGFR* mutations are altered in only 9.4% of patients with SCLC, and specifically L861Q has been rarely reported (2-5). *EGFR* exon 19 deletion mutation and *EGFR* exon 21 L858R point mutation are among the most commonly sensitizing mutations found. Transformation to SCLC occurs in 3–10% of *EGFR*-mutant NSCLC (5) and most cases of *EGFR*-mutated SCLC result from transformation, a scenario which may alter the approach to treatment (6). To our knowledge, there is no report of a shared *EGFR* L861Q mutation between two different sites representing NSCLC and SCLC. We present a patient with both NSCLC and SCLC, each harbouring the *EGFR* L861Q point mutation, and discuss the treatment implications of this mutation. We present this case in accordance with the CARE reporting checklist (available at <https://pcm.amegroups.com/article/view/10.21037/pcm-22-67/rc>).

## Case presentation

We present a case of a 78-year-old female with tobacco use in the past, who was found by screening mammogram to have right-sided bulky axillary lymphadenopathy and was

referred to the hospital for expedited work-up. Core needle biopsy of a right axillary lymph node was performed. The morphology showed a poorly differentiated malignancy, and immunohistochemistry was consistent with metastatic non-small cell carcinoma (*Figure 1*: top). <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT) demonstrated a 5.3 cm × 3.8 cm mass within the right lung, scattered pulmonary nodules, and lymphadenopathy in the chest, axillae, pelvis and retroperitoneum (*Figure 2A,2B*). <sup>18</sup>F-FDG PET/CT imaging also showed a right distal femur mass (*Figure 2C*), which was subsequently biopsied and showed pathologic features consistent with metastatic small cell carcinoma (*Figure 1*: bottom). Magnetic resonance imaging (MRI) of the brain identified multiple numerous enhancing lesions suggestive of leptomeningeal metastasis (*Figure 2D,2E*).

Next-generation sequencing (NGS) of biopsies from the lymph node and femur was performed to determine the relatedness of these malignancies and facilitate management decisions. Molecular profiling showed shared mutations in multiple genes: *PIK3CA*, *EGFR*, *TP53*, *NFKB1A*, and *NKX2-1* (*Table 1*). The patient completed 8/10 fractions of whole brain radiation as well as 5 fractions of radiation treatments to the right femur. The patient then started carboplatin AUC4 and etoposide 65 mg/m<sup>2</sup> to be given every three weeks. Unfortunately, anti-EGFR therapy was not able to be initiated in this patient as after only two cycles of chemotherapy, the patient was hospitalized with altered mental status and the identification by MRI of new metastasis. The patient decided to pursue comfort care and hospice without further treatment of her malignancy.

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). The patient provided written consent for this case report prior to her passing; however the form was lost. Telephone consent obtained from next of kin, spouse, who is in full support of the publication of this article. Consent form indicating the next of kin including contact information is available for review by the editorial office of this journal.

## Molecular tumor board discussion

The case was presented at the Northwell Health Molecular Tumor Board for discussion of the following consult questions.

### Highlight box

#### Key findings

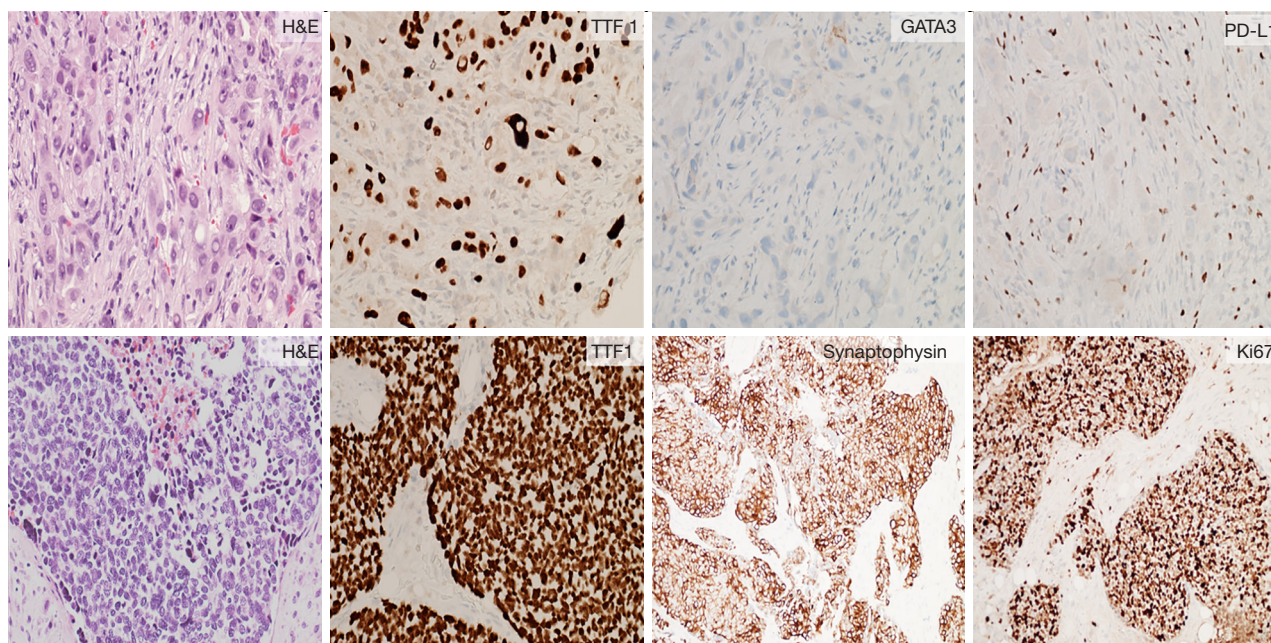
- Synchronous *EGFR* L861Q mutation within the SCLC and NSCLC biopsy results.

#### What is known and what is new?

- *EGFR* mutation commonly found within NSCLC.
- Unclear of the relevance and prevalence of an *EGFR* mutation in synchrony with a NSCLC and SCLC.

#### What is the implication, and what should change now?

- *EGFR* known as a driver mutation within NSCLC which could also be a therapeutic option if a synchronous SCLC with the same mutation is identified.



**Figure 1** Micrographs of axillary and right femur biopsy. Top row: NSCLC is shown in 4 micrographs. Ultrasound guided core biopsy from right axillary lymph node positive for metastatic poorly differentiated non-small cell adenocarcinoma (H&E, 400 $\times$ ). Positive for TTF1 (IHC TTF1, 400 $\times$ ), negative for GATA3 (IHC GATA3, 400 $\times$ ), most compatible with primary carcinoma of the lung. Less than 1% of tumor cells were positive for PD-L1 (IHC PD-L1, 400 $\times$ ). Bottom row: SCLC is shown in 4 micrographs. Resection from mass in the right femur showing nests of tumor cells with high nuclear-cytoplasmic ratio, salt-and-pepper chromatin pattern and absent nucleoli, consistent with metastatic small cell carcinoma of femur (H&E, 200 $\times$ ). The tumor cells are positive for TTF1 (IHC TTF1, 200 $\times$ ), synaptophysin (IHC synaptophysin, 100 $\times$ ), with variable Ki67 proliferative index (IHC Ki67, 100 $\times$ ) reaching approximately 80% in hot spot areas. Additional stains (not depicted in the image) showed the tumor cells are positive for cytokeratin CAM 5.2, and cytokeratin 7 and negative for chromogranin and cytokeratin 20. NSCLC, non-small cell lung cancer; TTF, thyroid transcription factor; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1; SCLC, small cell lung cancer; H&E, hematoxylin and eosin.

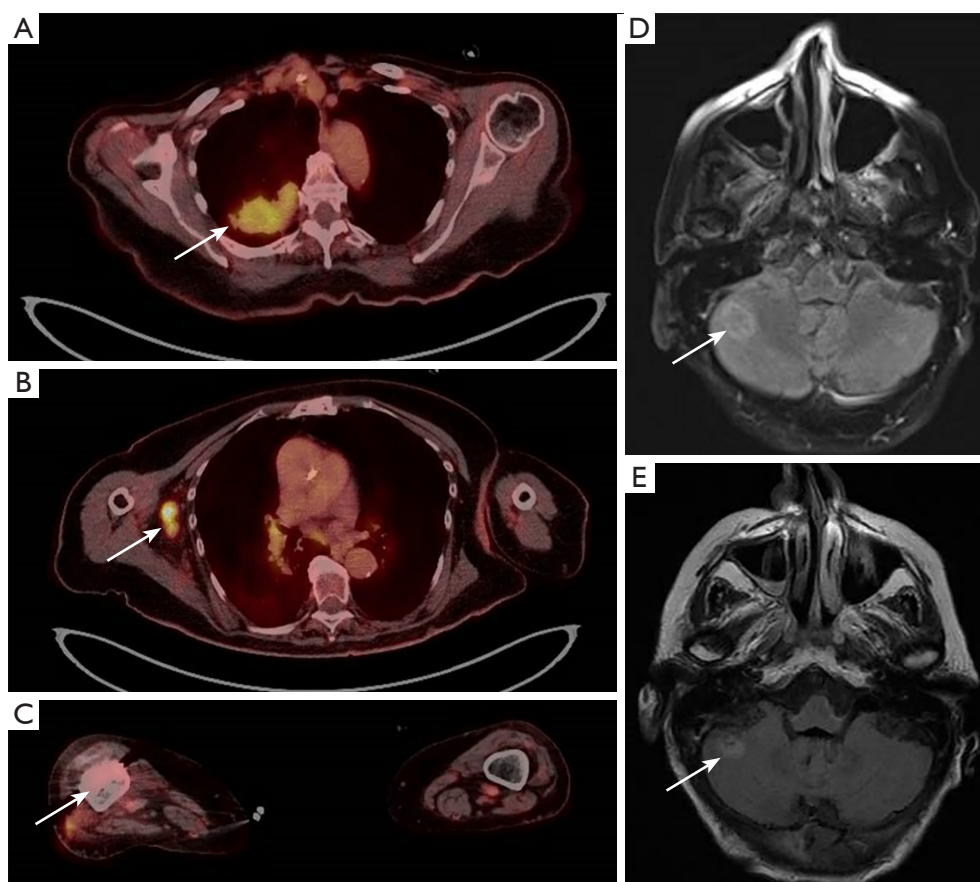
***Based on a review of the pathology, imaging, and molecular analysis, does the board believe the NSCLC and SCLC are more likely distinct primary malignancies or derived from a common origin? And, if the tumors share a common origin, are there any molecular features that would be consistent with transformation?***

The tumor board discussed the possibility of combined SCLC with NSCLC component, each harboring the *EGFR* L861Q mutation, with the SCLC component metastasizing to the femur and the NSCLC component metastasizing to the axillary node. However, the consensus was that the two lung cancers had a common origin given the preponderance of shared mutations, including the rare *EGFR* L861Q mutation, as well as the known ability of NSCLC to transform to SCLC (Table 1).

On the topic of transformation, it was discussed that

the femur biopsy demonstrated an *RB1* mutation, with a 78.5% allele frequency which is likely the driver mutation for the SCLC transformation. Literature review of tumor samples and cell lines derived from resistant *EGFR* mutant patients demonstrated that retinoblastoma (RB) is lost in 100% of these SCLC transformed cases but rarely in those that remain NSCLC (7) *RB1* inactivation is well known to play an important role in the tumorigenesis of SCLC (8,9). There have been many genomic alterations identified in SCLC including *RB* loss, *c-Kit* overexpression, telomerase activation, *c-Myc* amplification and *p53* mutation; however, *RB1* mutation or inactivation is a hallmark in SCLC (9). Therefore, the presence of the rare *EGFR* mutation and the presence of the *RB1* mutation were supportive evidence of transformation. It is important to note however there are reports of *EGFR*-mutation positive SCLC occurring without any preceding diagnosis of NSCLC (5).





**Figure 2** Original  $^{18}\text{F}$ -FDG PET/CT showing axillary lymphadenopathy, lung masses, femoral mass and CNS disease. (A) FDG avid lobulated contiguous posterior right upper lobe and superior segment right lower lobe lung mass, measured 5.3 cm  $\times$  3.8 cm on CT [86], SUV 8.0 (white arrow pointing to mass). (B) White arrow pointing to right axillary lymphadenopathy, 2.9 cm  $\times$  1.5 cm (image 106), SUV 11.5. (C) White arrow pointing to heterogeneous mild FDG avidity adjacent to the proximal portion and short linear FDG avidity along the medial aspect of the right mid/distal femur, SUV 6.5. (D) Multiple lesions identified with the largest being a peripherally enhancing lesion involving the right cerebellar measures approximately 2.2 cm  $\times$  1.5 cm as seen in the figure (white arrow). (E) Some lesions smaller in size and overall representing a mixed response to treated as demonstrated above involving the right cerebellar lesion now measuring 0.5 cm  $\times$  0.6 cm (white arrow). FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; CNS, central nervous system; CT, computed tomography; SUV, standardized uptake value.

The allele frequency of the shared *EGFR* L861Q mutation was 83% in the SCLC biopsy and 21.3% in the NSCLC biopsy. A possible explanation for this finding is that the transformation of the SCLC derived from a subclone of the NSCLC containing this mutation, and the SCLC subsequently developed a copy number amplification or loss of heterozygosity of the *EGFR* gene.

***What would be the predictive benefit for anti-EGFR directed therapy for this uncommon mutation?***

Tyrosine kinase inhibitors are effective treatments for

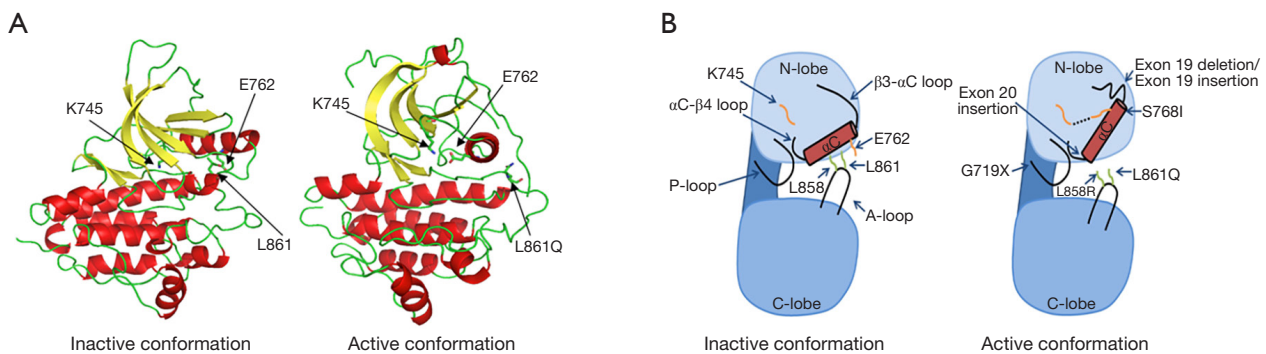
NSCLCs with *EGFR* mutations. The *EGFR* L861Q missense mutation arises from the nucleotide change c.2582T>A in exon 21, resulting in a substitution to glutamine from leucine at position 861 (*Figure 3A*) (10). The *EGFR*-L861Q mutation confers conformational changes leading to an active kinase form. The Leu-861 is packed in a hydrophobic core of the wild-type structure and switching to a polar residue triggers a conformational transition of the activation loop folding outwards, towards an active-like kinase state (*Figure 3*) (10,11).

In general, *EGFR* mutations in the kinase domain *EGFR* activate the kinase, sensitizing patients to treatment with

**Table 1** Molecular profile of non-small cell and small cell carcinoma including AF and AC

Site	LN	Femur
Histology	Non-small cell carcinoma	Small-cell carcinoma
Shared mutations	<i>PIK3CA</i> H1047L; AF: LN, 7.8%; bone, 87.3% <i>EGFR</i> L861Q; AF: LN, 21.3%; bone, 83% <i>TP53</i> P250L; AF: LN, 17.3%; bone, 80.5% <i>NFKBIA</i> amplification; AC: LN, 17; bone, 9 <i>NKX2-1</i> amplification; AC: LN, 28; bone, 10	
Unique mutations	<i>BARD1</i> splice site 1315-1G>C; AF: 10.3% <i>RAD21</i> amplification; AC: 12 <i>AKT1</i> amplification; AC: 23	<i>RB1</i> splice site 2107-1G>T; AF: 78.5% <i>BCL2L2</i> amplification; AC: 9 <i>ZNF217</i> amplification—equivocal; AC: 8 <i>GNAS</i> amplification—equivocal; AC: 8 <i>AURKA</i> amplification—equivocal; AC: 8
PDL-1 staining	<1% of tumor cells	Focal positivity in inflammatory/stromal cells

AF, Allele frequencies; AC, amplification copies; LN, lymph node; PD-L1, programmed death-ligand 1.



**Figure 3** Structural model (A) and carton model (B) of the *EGFR*-L861Q mutant. (A) Inactive conformation of *EGFR*. The position of L861 is indicated with an arrow. The salt bridge between K745 and E762 is broken in the inactive structure (10). (B) Active/mutant conformation of *EGFR*-L861Q: displays the active-like conformation of the activation loop. Note the new position of *EGFR*-L861Q residue. The restored salt bridge interaction between K745 and E762 are indicated with arrows in the structural model and dotted lines in the carton model. The *EGFR*-L861Q mutation confers conformational changes leading to an enhanced kinase activity (11). *EGFR*, epidermal growth factor receptor.

an *EGFR* inhibitor. Review of literature with this specific mutation, there is an associated response rate of 56% to afatinib and 40–60% with erlotinib or gefitinib (12–14) suggesting this patient may benefit from *EGFR* tyrosine kinase inhibitors. Early studies have shown that the L861Q mutation in particular displays enhanced kinase activity and transforming potential compared with other uncommon *EGFR* mutations, though it is not necessarily a drug-sensitizing mutation (15). Several clinical trials (16,17) have

shown an intermediate response rate to afatinib, though largely in the NSCLC setting.

Studies of L861Q in the Ba/F3 model system demonstrated that similar to S768I mutations, L861Q is resistant to first-generation *EGFR*i compared to L858R, but unlike S768I, L861Q was sensitive to both afatinib and osimertinib treatment (18). The esophageal cancer cell line KYSE270 that harbors an endogenous *EGFR* L861Q mutation also showed comparable results to the Ba/F3

model system (19). These data suggest that both second- and third-generation inhibitors may be effective at targeting L861Q mutations (11). Current phase II studies are ongoing to evaluate the use of osimertinib in patients with L861Q mutations and initial reports are promising with 77% of patients achieving a partial response (20-22).

### *What would be the most appropriate management for this patient with the molecular findings?*

Regarding the management plan, it was discussed whether imaging or molecular evidence could identify a substantial disparity in burden from either cancer type, which if found, might motivate treating the cancer type of greater burden. After extensive discussion at tumor board, the decision was made to proceed with treatment for the patient's SCLC given the more aggressive nature of this disease in general compared to NSCLC. Data supporting combining tyrosine kinase inhibitors and chemotherapy are sparse in the context of *EGFR* mutation positive co-occurring NSCLC and SCLC. Many large-scale phases III randomized controlled trials (23,24) have shown that adding chemotherapy to EGFR-tyrosine kinase inhibitors (EGFR-TKIs) did not improve survival benefit in NSCLC. While this observation could be related to the fact that these studies were not specific to *EGFR*-mutant NSCLC, a possible explanation for lack of benefit could be because of G1-phase cell-cycle arrest by EGFR-TKI which may in turn result in subdued efficacy of chemotherapy. On the contrary, recent studies (25) a large meta-analysis demonstrated that EGFR-TKI combined with chemotherapy has superior efficacy compared to EGFR-TKI alone in advanced *EGFR* mutated NSCLC. Therefore, adding a TKI to chemotherapy is still controversial and ongoing trials will hopefully answer this question with more clarity. Nevertheless, the combination has been shown to be more toxic in multiple studies, compared to chemotherapy or TKI alone and for our patient with performance status (PS) of 2, we wanted to make sure to provide a treatment that was urgently needed with plans to add afatinib after completion of four cycles of chemotherapy.

### Conclusions

Molecular interrogation is a valuable tool to identify shared origin of synchronous malignancies. This case demonstrates synchronous NSCLC and SCLC disease whose etiology was elucidated using molecular profiling as an *RBI* mutation

is often observed in transformed SCLC, and the rare *EGFR* mutation is not reported in *de novo* SCLC but is found, albeit uncommonly, in NSCLC.

*EGFR* is a well-studied driver mutation which can be targeted. This case had an *EGFR* L861Q mutation in which tyrosine kinase inhibitors that have shown efficacy. Given this patient had a mutation that can be targeted which was harbored in both SCLC and NSCLC, treatment options included the addition of targeted treatment along with chemotherapy. Unfortunately, the patient progressed prior to initiation of anti-EGFR therapy and pursued hospice. This case represents the importance of molecular profiling and testing especially when there are two different histologic pathologies. The case presented provides a platform for academic discussion and highlights the importance of molecular tumor board discussions which can assist with guiding treatment.

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### Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <https://pcm.amegroups.com/article/view/10.21037/pcm-22-67/rc>

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://pcm.amegroups.com/article/view/10.21037/pcm-22-67/coif>). The authors have no conflicts of interest to declare.

*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. 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). The patient provided written consent for this case report prior to her passing; however the form was

lost. Telephone consent obtained from next of kin, spouse, who is in full support of the publication of this article. Consent form indicating the next of kin including contact information is available for review by the editorial office of this journal.

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