

World Journal of *Clinical Cases*

World J Clin Cases 2022 March 26; 10(9): 2660-2975



REVIEW

- 2660 Role of metabolites derived from gut microbiota in inflammatory bowel disease
Zheng L, Wen XL, Duan SL

MINIREVIEWS

- 2678 Roles of Wnt/ β -catenin signaling pathway related microRNAs in esophageal cancer
Chu CY, Wang R, Liu XL
- 2687 Animal models applied to acute-on-chronic liver failure: Are new models required to understand the human condition?
Gama JFG, Cardoso LMDF, Lagrota-Candido JM, Alves LA

ORIGINAL ARTICLE**Case Control Study**

- 2700 Associations between coagulation factor XII, coagulation factor XI, and stability of venous thromboembolism: A case-control study
Meng Y, Li Y, Ye YJ, Ma Q, Zhang JB, Qin H, Deng YY, Tian HY

Retrospective Cohort Study

- 2710 Nomogram to predict the risk of endoscopic removal failure with forceps/baskets for treating submandibular stones
Huang Y, Liang PS, Yang YC, Cai WX, Tao Q
- 2721 Association between anesthesia technique and complications after hip surgery in the elderly population
Guo LS, Wang LN, Xiao JB, Zhong M, Zhao GF

Retrospective Study

- 2733 Perforating and nonperforating indications in repeated surgeries for Crohn's disease
Shen WS, Huang XH, Liu RQ, Li CY, Li Y, Zhu WM
- 2743 Treatment of *Pneumocystis jirovecii* pneumonia in non-human immunodeficiency virus-infected patients using a combination of trimethoprim-sulfamethoxazole and caspofungin
Wu HH, Fang SY, Chen YX, Feng LF
- 2751 Acute kidney injury in traumatic brain injury intensive care unit patients
Huang ZY, Liu Y, Huang HF, Huang SH, Wang JX, Tian JF, Zeng WX, Lv RG, Jiang S, Gao JL, Gao Y, Yu XX
- 2764 Enucleation combined with guided bone regeneration in small and medium-sized odontogenic jaw cysts
Cao YT, Gu QH, Wang YW, Jiang Q

Clinical Trials Study

- 2773 Determination of the ED₉₅ of intranasal sufentanil combined with intranasal dexmedetomidine for moderate sedation during endoscopic ultrasonography

Zou Y, Li N, Shao LJZ, Liu FK, Xue FS, Tao X

Observational Study

- 2783 Overexpression of Ubiquilin4 is associated with poor prognosis in patients with cervical cancer

Wang LN, Huang KJ, Wang L, Cheng HY

Randomized Clinical Trial

- 2792 Peplau's interpersonal relationship theory combined with bladder function training on patients with prostate cancer

Yang XH, Wu LF, Yan XY, Zhou Y, Liu X

SYSTEMATIC REVIEWS

- 2801 Efficacy of bone grafts in jaw cystic lesions: A systematic review

Wang J, Yao QY, Zhu HY

CASE REPORT

- 2811 Short stature associated with a novel mutation in the aggrecan gene: A case report and literature review

Yin LP, Zheng HX, Zhu H

- 2818 Treatment with sorafenib plus camrelizumab after splenectomy for primary splenic angiosarcoma with liver metastasis: A case report and literature review

Pan D, Li TP, Xiong JH, Wang SB, Chen YX, Li JF, Xiao Q

- 2829 Sarcomatoid intrahepatic cholangiocarcinoma with good patient prognosis after treatment with Huaier granules following hepatectomy: A case report

Feng JY, Li XP, Wu ZY, Ying LP, Xin C, Dai ZZ, Shen Y, Wu YF

- 2836 Sequential occurrence of T790M mutation and small cell lung cancer transformation in EGFR-positive lung adenocarcinoma: A case report

Hong E, Chen XE, Mao J, Zhou JJ, Chen L, Xu JY, Tao W

- 2844 Early diagnosis of Gitelman syndrome in a young child: A case report

Wu CY, Tsai MH, Chen CC, Kao CH

- 2851 Congenital intestinal malrotation with gastric wall defects causing extensive gut necrosis and short gut syndrome: A case report

Wang Y, Gu Y, Ma D, Guo WX, Zhang YF

- 2858 Delusional parasitosis as premotor symptom of parkinson's disease: A case report

Oh M, Kim JW, Lee SM

- 2864** Laninamivir-induced ischemic enterocolitis: A case report
Suzuki C, Kenzaka T
- 2871** Intramural pregnancy after *in vitro* fertilization and embryo transfer: A case report
Xie QJ, Li X, Ni DY, Ji H, Zhao C, Ling XF
- 2878** Bilateral ureteral reimplantation in a patient with an intraperitoneal ectopic bipenis: A case report
Jia YT, Shi BL, Zhang J, Li YY, Zhu J
- 2883** Lumbar disc sequestration mimicking a tumor: Report of four cases and a literature review
Li ST, Zhang T, Shi XW, Liu H, Yang CW, Zhen P, Li SK
- 2895** Parasitic leiomyoma in the trocar site after laparoscopic myomectomy: A case report
Roh CK, Kwon HJ, Jung MJ
- 2901** Giant nontraumatic myositis ossificans in a child: A case report
Xia AN, Wang JS
- 2908** Paradoxical carbon dioxide embolism during laparoscopic hepatectomy without intracardiac shunt: A case report
Jeon S, Hong JM, Lee HJ, Kim Y, Kang H, Hwang BY, Lee D, Jung YH
- 2916** Local hyperthermia combined with chemotherapy for the treatment of multiple recurrences of undifferentiated pleomorphic sarcoma: A case report
Zhou YT, Wang RY, Zhang Y, Li DY, Yu J
- 2923** Acute coronary artery stent thrombosis caused by a spasm: A case report
Meng LP, Wang P, Peng F
- 2931** Turner syndrome with primary myelofibrosis, cirrhosis and ovarian cystic mass: A case report
Xu LW, Su YZ, Tao HF
- 2938** Esophageal myoepithelial carcinoma: Four case reports
Lu H, Zhao HP, Liu YY, Yu J, Wang R, Gao JB
- 2948** Ipsilateral hemifacial microsomia with dextrocardia and pulmonary hypoplasia: A case report
Guo R, Chang SH, Wang BQ, Zhang QG
- 2954** Upper gastrointestinal bleeding from a Mallory-Weiss tear associated with transesophageal echocardiography during successful cardiopulmonary resuscitation: A case report
Tang MM, Fang DF, Liu B
- 2961** Malignant struma ovarii with papillary carcinoma combined with retroperitoneal lymph node metastasis: A case report
Xiao W, Zhou JR, Chen D

- 2969** Occult colon cancer with sepsis as the primary manifestation identified by bone marrow puncture: A case report

Wang HJ, Zhou CJ

ABOUT COVER

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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Sequential occurrence of T790M mutation and small cell lung cancer transformation in EGFR-positive lung adenocarcinoma: A case report

Er Hong, Xi-Er Chen, Jia Mao, Jing-Jing Zhou, Ling Chen, Jia-Yi Xu, Wei Tao

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Abstract

BACKGROUND

The emergence of secondary drug resistance when treating epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) using EGFR-tyrosine kinase inhibitors (EGFR-TKIs), seriously affects the therapeutic efficacy and survival of patients. Here, we report a case of advanced NSCLC focusing on the application of multiple biopsy modalities to reveal the development of multiple resistance mechanisms during targeted therapies.

CASE SUMMARY

A 54-year-old male patient presented with EGFR 19Del-mutated advanced lung adenocarcinoma, and exhibited the development of a T790M mutation during initial TKI treatment. Following 3 mo of Osimertinib treatment, a mixed response was observed. Tissue biopsy of the progressive lesion showed transformation to small cell lung cancer (SCLC) harboring RB1 and TP53 mutations, with loss of the original T790M mutation. A standard chemotherapy regimen with Anlotinib for SCLC was administered. Repeat biopsy revealed adenocarcinoma combined with SCLC after tumor progression. The patient's overall survival was 24 mo.

CONCLUSION

Multiple biopsy modalities can reveal the development of multiple resistance mechanisms which help with treatment decision-making. Comprehensive treatment regimens according to the drug resistance mechanism significantly improved the prognosis of such patients.

Key Words: Adenocarcinoma; Epidermal growth factor receptor-tyrosine kinase inhibitor; Epidermal growth factor receptor-T790M mutation; Small cell lung cancer transformation; Chemotherapy; Case report

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Core Tip: The emergence of secondary drug resistance seriously affects the efficacy of tyrosine kinase inhibitor (TKI) treatment and prognosis of patients with epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer. EGFR-T790M mutation and tumor phenotype transformation are common drug resistance mechanisms in the first-generation TKI treatment process. Thus, it is necessary to determine the potential mechanisms using multiple biopsy methods with the aim of selecting appropriate and effective therapeutic drugs and extending the survival of patients with lung cancer.

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INTRODUCTION

Lung carcinoma remains a principal reason for cancer-associated mortality worldwide. However, the treatment strategies for lung cancer, particularly those for non-small cell lung cancer (NSCLC) have undergone revolutionary advancement alongside the emergence of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). Within the kinase domain of EGFR, these activating mutations, particularly the deletion of exon 19 as well as the mutation in exon 21 (L858R), occur in 10%-15% of Caucasian patients with lung adenocarcinoma and in up to 50% of patients of Asian origin[1]. Gefitinib and Erlotinib, which are first-generation EGFR-TKIs or Dacomitinib and Afatinib, which are second-generation EGFR-TKIs, have been recommended as the first-line treatment strategy for EGFR mutation-positive NSCLC. Although their effectiveness, as well as safety, have been continuously proven, unfortunately, acquired resistance inevitably emerges, which typically occurs after a median period of 9.2-14.7 mo of TKIs therapy[2]. Three mechanistic categories of acquired resistance have been identified: Bypass signaling pathway activation, target gene mutation and histological transformation[3]. For first-generation EGFR-TKIs, a mutation in EGFR-T790M is the primary mechanism regulating acquired resistance, and is observed in nearly 50%-60% of cases, while 10% of tumors exhibiting EGFR-TKIs resistance transform to small cell lung cancer (SCLC) morphology[2].

Herein, we report a case of NSCLC with EGFR-T790M mutation and conversion to SCLC while treated with EGFR-TKIs. The patient underwent comprehensive treatment, including targeted therapy, platinum-containing chemotherapy, antiangiogenic therapy and immunotherapy, with an overall survival of 24 mo.

CASE PRESENTATION

Chief complaints

A 54-year-old male patient presented to the hospital with dyspnea and productive cough on November 5, 2016, without fever, hemoptysis and pleuritic pain.

History of present illness

The patient had continuously reported symptoms which had persisted for more than 5 mo and were gradually aggravated.

History of past illness

The patient had a history of pulmonary tuberculosis with no history of smoking or malignant tumors.

Personal and family history

The patient denied any relevant personal and family history.

Physical examination

Physical examination showed that the patient's body temperature was 36.6°C, pulse rate was 84 bpm, blood pressure was 126/77 mmHg, respiratory rate was 18 breaths/min, and performance status was 0.

Laboratory examinations

The laboratory results were normal except that the carcinoembryonic antigen (CEA) level was 128.51 ng/mL (the normal range: 0-5.0 ng/mL).

Imaging examinations

Computed tomography (CT) on November 5, 2016 revealed a 38 mm × 48 mm tumor in the upper right lobe, with multiple pleural and bilateral pulmonary metastases, mediastinal, and hilar lymphadenopathy (Figure 1A). Cranial magnetic resonance imaging, abdominal ultrasound, and bone emission CT were carried out to confirm the absence of distant metastases.

Pathology and genetic testing

Trans-bronchial biopsy confirmed lung adenocarcinoma on November 10, 2016. Immunohistochemical analysis showed positive immunostaining for cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF-1) and negative immunostaining for the tumor protein 63 (P63), cytokeratin 5/6 (CK5/6) and synaptophysin (Syn) (Figure 2A). The amplification refractory mutation system technique identified EGFR exon 19 deletion.

FINAL DIAGNOSIS

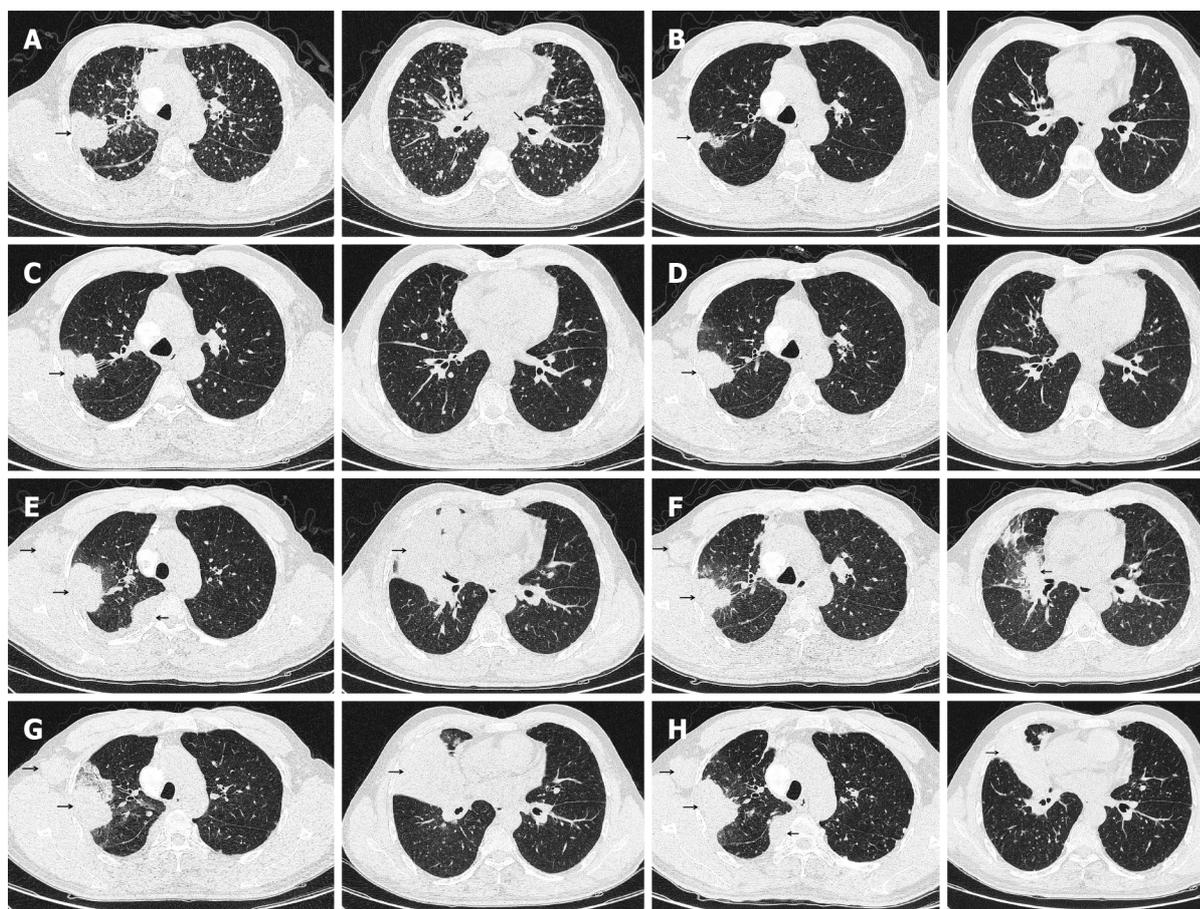
The patient was diagnosed with stage IV right lung adenocarcinoma bearing a mutation caused by EGFR exon 19 deletion (cT2bN3M1a in accordance with version 8 of TNM staging).

TREATMENT

As a first-line treatment, 250 mg of oral Gefitinib was administered once a day starting on November 17, 2016. As per the solid tumor version 1.1 (RECIST 1.1) response evaluation criteria, the best efficacy evaluation was a partial response (PR) after 4 mo (Figure 1B). Serum CEA level significantly decreased to 27.16 ng/mL on March 6, 2017 (Figure 3). After 10.5 mo of progression-free survival (PFS), disease progression was confirmed by CT of the chest on September 3, 2017, which demonstrated an enlarged right upper lobe mass and increased metastatic nodules (Figure 1C). Droplet digital PCR (ddPCR) assay was employed to verify the distinct plasma EGFR-T790M. The therapeutic drug AZD9291 (80 mg daily), also known as Osimertinib, was used as a second-line treatment on October 4, 2017. Unexpectedly, a mixed response was observed after 1 mo, with a growing right upper lobe lesion but the near disappearance of pulmonary metastases (Figure 1D).

Following 3 mo of Osimertinib treatment, chest CT showed a further enlargement of the right upper lobe lesion (58 mm × 36 mm), a sizable mass in the right lung situated in the middle lobe, a local pleural mass with rib destruction, and an enlarged right axillary lymph node (34 mm × 36 mm) on January 5, 2018 (Figure 1E), following a 3.0 mo PFS. Blood tests showed an increase in the serum level of neuron-specific enolase (NSE) to 22.4 ng/mL and persistent decreasing levels of CEA to 16.70 ng/mL (Figure 3). Biopsy of the progressive right upper lobe mass was repeated and showed SCLC transformation according to immunohistochemistry (IHC) and revealed the following: positive Syn and TTF-1 expression, and NapsinA-negative (Figure 2B). Tissues were obtained for next-generation sequencing (NGS) using a panel consisting of 80 genes (3D Medicines, Shanghai, China), which revealed EGFR Exon19 (mutant abundance 58.00%), RB1 (mutant abundance 43.60%), TP53 (mutant abundance 82.60%) mutation and disappearance of EGFR-T790M. Intravenous etoposide 100 mg/m² from the 1st d to the 3rd d, in combination with carboplatin (EC) (with an area of 5 mg/mL/min under the concentration-time curve, administered intravenously every 21 d on day 1) was used as a third-line treatment. Following the four chemotherapy cycles, the serum NSE level markedly decreased to 5.5 ng/mL (Figure 3), and efficacy evaluation was a partial response (Figure 1F). Unfortunately, the disease progressed after six cycles of EC on June 25, 2018 (Figure 1G). The patient attained a PFS of 5 mo. Oral Anlotinib (12 mg/d, from day 1 to day 14, 21 d) plus 75 mg/m² docetaxel (injected intravenously on day 1) and intravenous carboplatin (5 mg/mL/min area under the concentration-time curve every 21 d on day 1) were administered as a fourth-line treatment. Lung lesions were stable for more than 3 mo (Figure 1H).

A CT-guided needle puncture of the lesion that had enlarged in size in the upper lobe of the right lung was obtained as the fourth biopsy on September 28, 2018 to monitor progression. Interestingly, the morphology of the lung mass showed poorly differentiated mixed histological subtypes of adenocarcinoma and SCLC (Figure 2C). The IHC staining data revealed the following: partially Syn-positive, partially CgA-positive, partially CD56-positive, partially NapsinA-positive, and PD-L1 < 1% (clone



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Figure 1 Transformation of chest computed tomography following various regimens. A: The baseline findings on chest computed tomography; B: Partial response (PR) after oral gefitinib 250 mg daily for 4 mo; C: Enlarged lesion in the right upper lobe and increased metastatic nodules after oral gefitinib 250 mg daily for 10.5 mo; D: Enlarged lesion in the right upper lobe with near disappearance of metastasis after oral Osimertinib 80 mg daily for 1 mo; E: Progressive disease (PD) after oral osimertinib 80 mg daily for 3 mo; F: PR after 4 cycles of etoposide + carboplatin; G: PD after 6 cycles of etoposide + carboplatin; H: Stable disease following 4 cycles of docetaxel + carboplatin + anlotinib.

22C3, DAKO, Agilent, Santa Clara, CA, United States). Tissue samples were detected *via* NGS containing a panel consisting of 420 genes (3D Medicines, Shanghai, China), which revealed EGFR Exon19 (mutant abundance: 38.28%), RB1 (mutant abundance: 68.48%), TP53 (mutant abundance: 76.97%) and tumor mutation burden (TMB): 9.68 Muts/Mb. Nivolumab was added to the previous therapeutic options as a fifth-line treatment on November 1, 2018 (180 mg intravenously every 2 wk). The entire treatment process is illustrated in [Figure 4](#).

OUTCOME AND FOLLOW-UP

Unfortunately, although the patient underwent the best supportive care due to continuous deterioration in his general condition after 2 cycles of a previous combination treatment (performance status score > 2), he died on December 22, 2018.

DISCUSSION

The inevitable emergence of acquired drug resistance seriously affects the prognosis of patients with NSCLC and mutations having EGFR-sensitivity. The median time to disease progression after initial TKI treatment is 10.2 mo and the most common symptoms are cough and dyspnea[4]. Various mechanisms of acquired resistance can be categorized such as the activation of alternative signaling pathways, secondary mutations in EGFR, and phenotypic or histologic transformation[5-7]. EGFR-T790M mutation is the most common mechanism of acquired resistance, and amounts to 50-60% of resistance acquired during primary EGFR-TKIs therapy[8]. Evaluation of EGFR T790M status is imperative for the establishment of first- or second-generation TKI-acquired drug resistance, which is

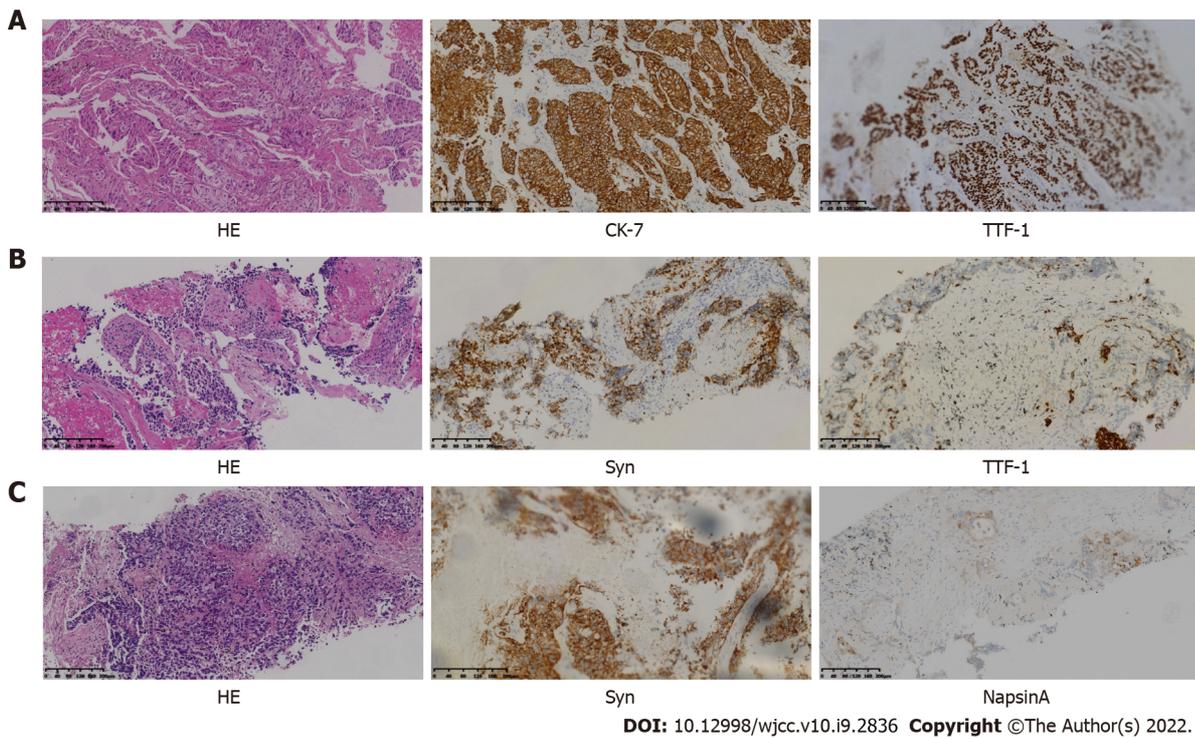


Figure 2 Changes in pathological morphology and immunohistochemistry. A: November 5, 2016, indicated adenocarcinoma, immunohistochemistry (IHC): CK-7+++; TTF-1+++; B: January 5, 2018, resistance to osimertinib, indicated small cell lung cancer, IHC: Syn+, TTF-1+; C: September 28, 2018, resistance to docetaxel + carboplatin + Anlotinib, suggested adenocarcinoma and small cell lung cancer, IHC: Syn+, NapsinA+. Magnification ×100.

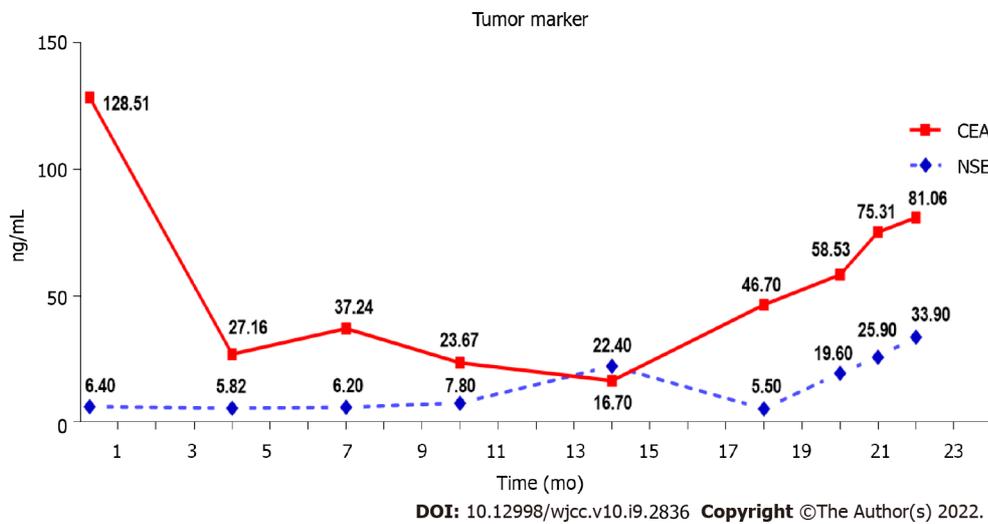
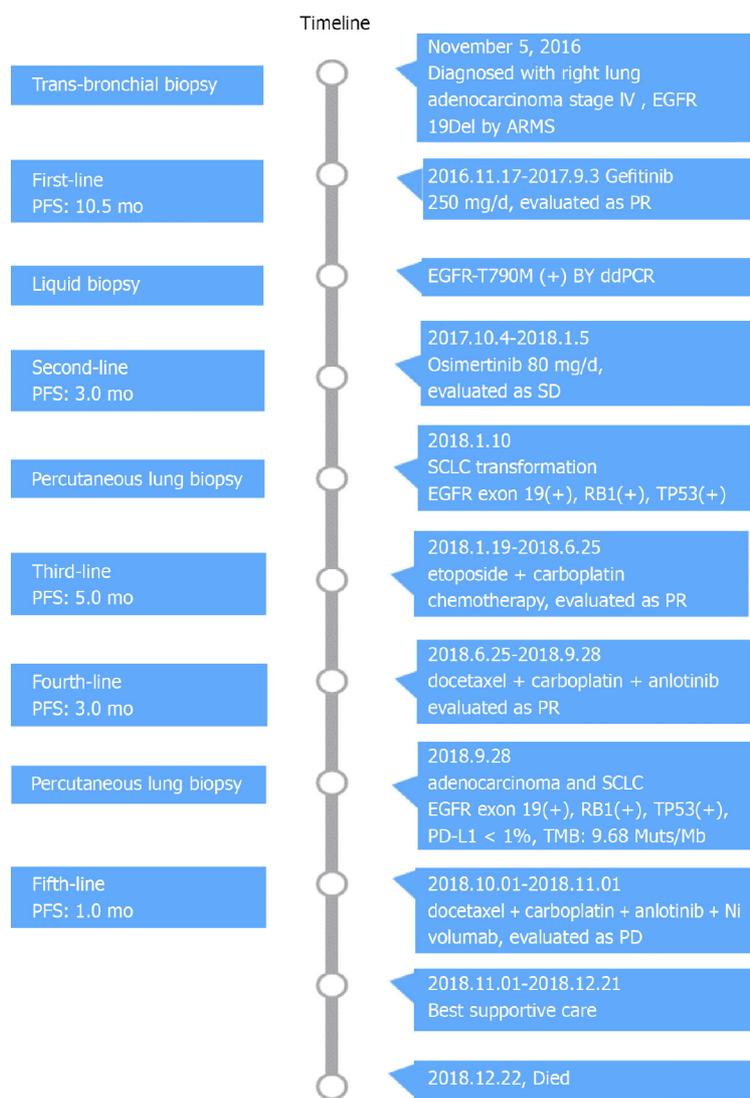


Figure 3 Fluctuations in serum carcinoembryonic antigen and neuron-specific enolase. NSE: neuron-specific enolase; CEA: carcinoembryonic antigen.

required for the selection of subsequent therapies and later proceeding to clinical trials. Recently, liquid biopsy genotyping of circulating tumor DNA (ctDNA) has become an attractive substitute to re-biopsy of tissues, due to its many potential advantages in comparison to tissue biopsy, such as improved safety of patients, reduced costs, shortened turnaround time, and counteracting the heterogeneity of different metastatic lesions[9]. A prospective study revealed that T790M detection based on ctDNA-using ddPCR was up to 77.1% sensitive, with a specificity of 63.2% and a positive predictive value of 79.0%, which indicated an acceptable correlation between tissue re-biopsy and ctDNA[10,11]. Due to the presence of tumor heterogeneity, the entire mechanism for resistance cannot be represented by a single tumor biopsy technique.

The scientific community has increasingly acknowledged that EGFR-mutant NSCLC can undergo SCLC transformation[12]. The conversion of tumor phenotype has been demonstrated to be a target-independent drug resistance mechanism. For patients with unsuccessful EGFR-TKIs treatment, up to



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Figure 4 Timeline of our case's treatment with multiline therapy.

10% of tumors have transformed into SCLC[8,13]. These transformed tumor cells show similar molecular characteristics to SCLC, including the disappearance of TP53 and RB activity[14,15]. Interestingly, these transformed tumors still possess the original EGFR mutation, with a marked reduction in the expression of EGFR, which may suggest that the EGFR signaling pathway is no longer the driving force for the origination of these tumors[14].

In our case, the patient who had advanced lung adenocarcinoma with EGFR 19Del was treated with Gefitinib for a period of 10.0 mo and developed secondary drug resistance. Osimertinib (third-generation TKI) was administered as the second-line TKI treatment at the time of detection of plasma T790M. A dramatic clinical response was observed during treatment with Osimertinib. The main lesion in the right upper lung continued to progress but the metastatic lesions in both lungs significantly regressed. Pathology of the upper right lung lesion biopsy indicated SCLC transformation. The EGFR Exon19 mutation was persistent, while T790M mutation had disappeared as shown by NGS, accompanied by the concurrence of RB1 and TP53 mutations. The above findings suggest that tumor cells tend to successively develop target-dependent and target-independent drug resistance mechanisms due to tumor heterogeneity and TKI selection pressure.

Marcoux *et al*[12] recently reported the largest retrospective investigation comprising 58 patients bearing EGFR-mutant NSCLC that exhibited transformation into SCLC following one or more types of EGFR-TKIs treatments. The median overall survival from the time of diagnosis was found to be 31.5 mo (24.8 to 41.3 mo, 95%CI), whereas the median survival time from the initiation of SCLC transformation was 10.9 mo (8.0 to 13.7 mo, 95%CI). Following transformation, clinical behavior was identical to classical SCLC in many aspects, with responses to taxanes and platinum-etoposide except for immune checkpoint inhibitors. There is still insufficient evidence for a standard therapy for relapsed SCLC. The unique TKI, Anlotinib has a highly selective inhibitory impact on multiple targets, particularly on

fibroblast growth factor receptor, stem cell growth factor receptor (c-Kit), vascular endothelial growth factor receptor, and platelet-derived growth factor receptors, and can inhibit tumor angiogenesis and tumor growth. The outcomes of the ALTER1202 study showed that compared to the placebo arm (4.1 mo *vs* 0.7 mo; HR = 0.19; 0.12-0.32; $P < 0.0001$, 95%CI), the median PFS in the Anlotinib arm was considerably prolonged, which should be considered as further-line treatment[16,17]. In our case, the response duration for this patient with PR was 5.0 mo, who underwent six cycles of etoposide plus carboplatin after SCLC transformation. The response to treatment for relapsed SCLC with Anlotinib in combination with docetaxel and carboplatin chemotherapy was more than 3.0 mo. Unfortunately, his disease responded less well to Nivolumab. The length of time from the initial diagnosis to transformation was almost 14.0 mo and the patient's overall survival duration was 24.0 mo.

CONCLUSION

We report a patient with sequential occurrence of multiple drug resistance after treatment with gefitinib. Comprehensive treatment regimens according to the drug resistance mechanism significantly improved the prognosis of this patient, including the EGFR-TKIs (Gefitinib, Osimertinib), chemotherapy, antiangiogenic drugs and immunotherapy. In summary, for the majority of patients with TKI-resistance, the resistance mechanisms are largely unknown. Repeated biopsies and application of the dynamic technique for multiple biopsies could disclose more comprehensive resistance mechanisms. Therefore, optimal therapy may be determined accordingly by increasing treatment efficacy and prolonging the duration of survival.

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FOOTNOTES

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