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Case Report

Dramatic response to an mTOR inhibitor in a Chinese patient with lung squamous cell carcinoma with an *mTOR* mutation and *PIK3CA* amplification: a case report

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Abstract: Activation of the PI3K/Akt/mTOR signaling pathway can promote tumor invasion and metastasis. Everolimus which is an *mTOR* inhibitor might thus have anti-tumor effects. Everolimus has achieved good results when used to treat breast cancer patients with PI3K/AKT/mTOR pathway mutations. However, there are no reports indicating that everolimus is effective for first-line treatment of squamous cell lung cancer (SQCLC). Here, a 70-year-old Chinese patient with SQCLC is reported where next-generation sequencing (NGS) revealed an *mTOR* mutation and *PIK3CA* amplification. The patient had a partial response to everolimus treatment. These findings may provide a basis for the further clinical exploration of targeted therapies in SQCLC with *mTOR* mutations.

Keywords: Squamous cell lung cancer, targeted therapy, *mTOR* mutation, *PIK3CA* amplification, everolimus

Introduction

Lung cancer is one of the most common human malignancies worldwide. Indeed, lung cancer is the number one cause of cancer-related deaths. Approximately 80%-85% of patients diagnosed with lung cancer have non-small cell lung cancer (NSCLC), and of those patients, 20-30% have squamous cell lung cancer (SQCLC), which is a common pathologic subtype of NSCLC [1-3]. As the field of cancer genomics has expanded, it has been shown that *EGFR*, *PIK3CA, FGFR1, DDR2, PTEN, BRAF*, *MET*, and *IGF-1R* play important roles in the development of SQCLC. The rates of successful treatment and survival are worse for patients with SQCLC than for patients with lung adenocarcinoma. Imbalances in PI3K/Akt/mTOR signaling and abnormal activation of mTOR are common in a variety of tumors, including prostate cancer, pituitary cancer, NSCLC, ovarian cancer, and cervical cancer [3]. With respect to NSCLC, *PIK3CA* amplification leads to activation of the PI3K signaling pathway. The intensity of activation of the PI3K signaling pathway is greater in patients with SQCLC than in patients with lung adenocarcinoma. The activation of the PI3K signaling pathway can lead to a higher tumor grade and more rapid disease progression in patients with NSCLC. There is still insufficient clinical research to clarify the relationship between gene mutations that induce the activation of the PI3K/Akt/mTOR signaling pathways in tumors and the sensitivity of the tumors to *mTOR* inhibitors. However, *mTOR* inhibitors remain the primary treatment method for deregulated PI3K/Akt/mTOR signaling in tumors [4, 5]. Currently, there is limited clinical evidence regarding the use of targeted therapy in patients with SQCLC. Herein is reported a case of advanced SQCLC in a patient with an *mTOR* S2215T mutation and *PIK3CA* amplification. The tumor volume was significantly reduced one month after first-line treatment with everolimus, and the efficacy evaluation revealed a partial response (PR). Currently, the treatment has been ongoing for 10 months. This is the first report involving a patient with SQCLC with dual mutations of the PI3K/Akt/mTOR pathway who was treated with a single drug, namely, the mTOR inhibitor everolimus.

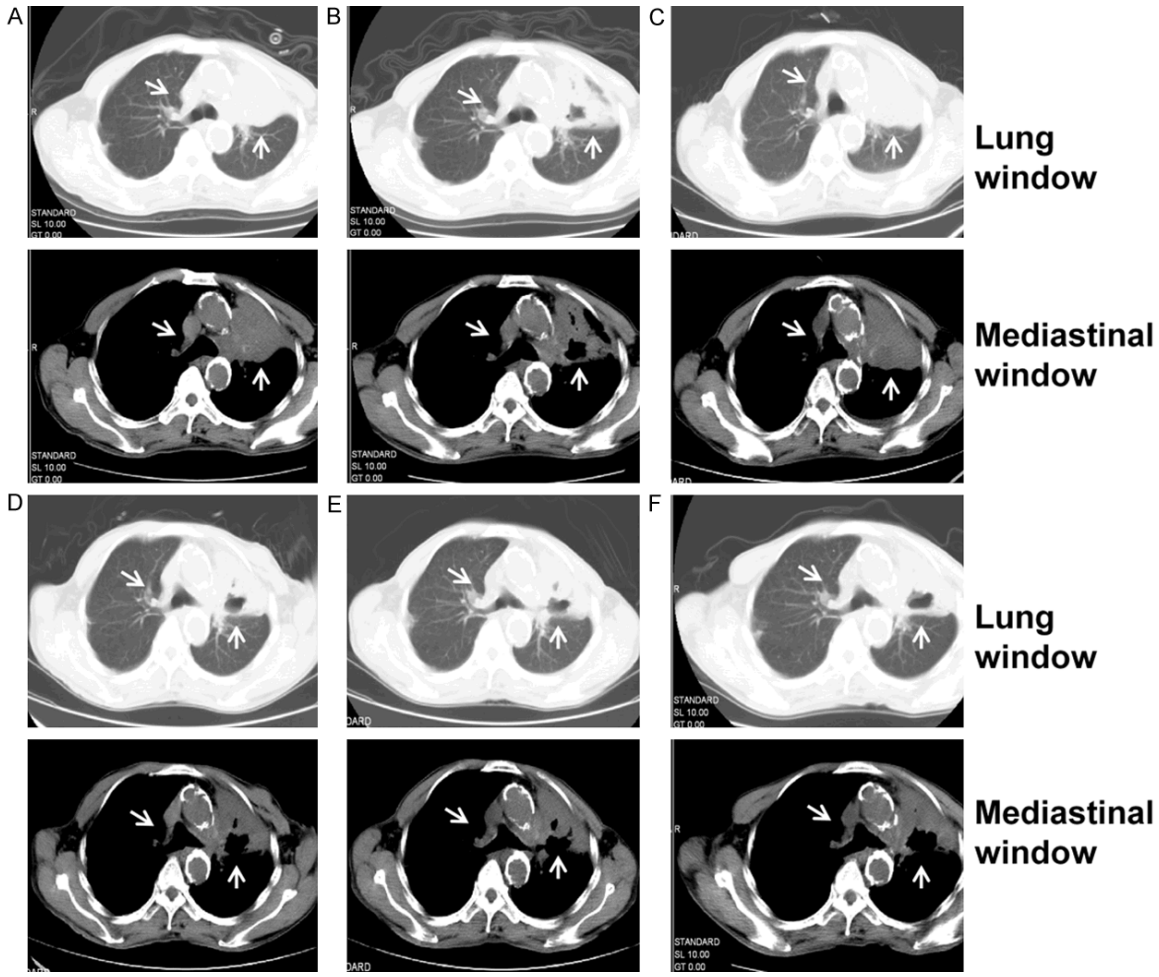

Figure 1. CT scans. (A) Baseline CT images revealed multiple lymph node metastases around the region of aorticopulmonary window and left hilar. (B) CT scan showed partial response after everolimus treatment for one month. (C) CT scan showed progressive disease after everolimus treatment for five months. (D) CT scan showed partial response after everolimus treatment for six months. CT scan showed sustained response after everolimus treatment for seven months (E) and eight months (F).

Case presentation

A 70-year-old male with a >50-year history of smoking cigarettes was diagnosed with SQCLC of the left lung (T4N2M1) in June 2016. A chest CT suggested that the mediastinum was involved, with a central-type carcinoma in the left lung and bilateral axillary lymphadenopathy. In February 2017, the patient was re-evaluated by a physician for dysphonia. The levels of the tumor markers CA-125 and CYF212 were increased to 48.71 U/ml (reference 0-35 U/ml) and 9.370 ng/ml (reference 0-3.3 ng/ml), respectively. The postoperative pathologic examination of a specimen obtained by a percutaneous left lung biopsy revealed moderately differentiated SQCLC. Immunohistochemistry revealed the following results: TTF-1 (-), CK7 (-), CK (+), NapsinA (-), P40 (+), P63 (+), CK5/6 (+), P53 (-), Ki-67 (positive index of 61%), Pgp (-), TopoII (grade II), GST-II (+++) and SP-A (-). The patient declined chemotherapy and thus underwent general symptomatic treatment and was discharged in stable condition. After 20 days, oral ulcers with a burning sensation that affected eating, a temperature of 38°C and persistent dysphonia with cough and a small amount of white phlegm were present. The patient's other vital signs and the results of the cardiovascular and nervous system examinations were normal. A chest CT showed multiple lymph node metastases around the region of aorticopulmonary window and left hilar on March 20, 2017 (**Figure 1A**). To further establish a diagno-

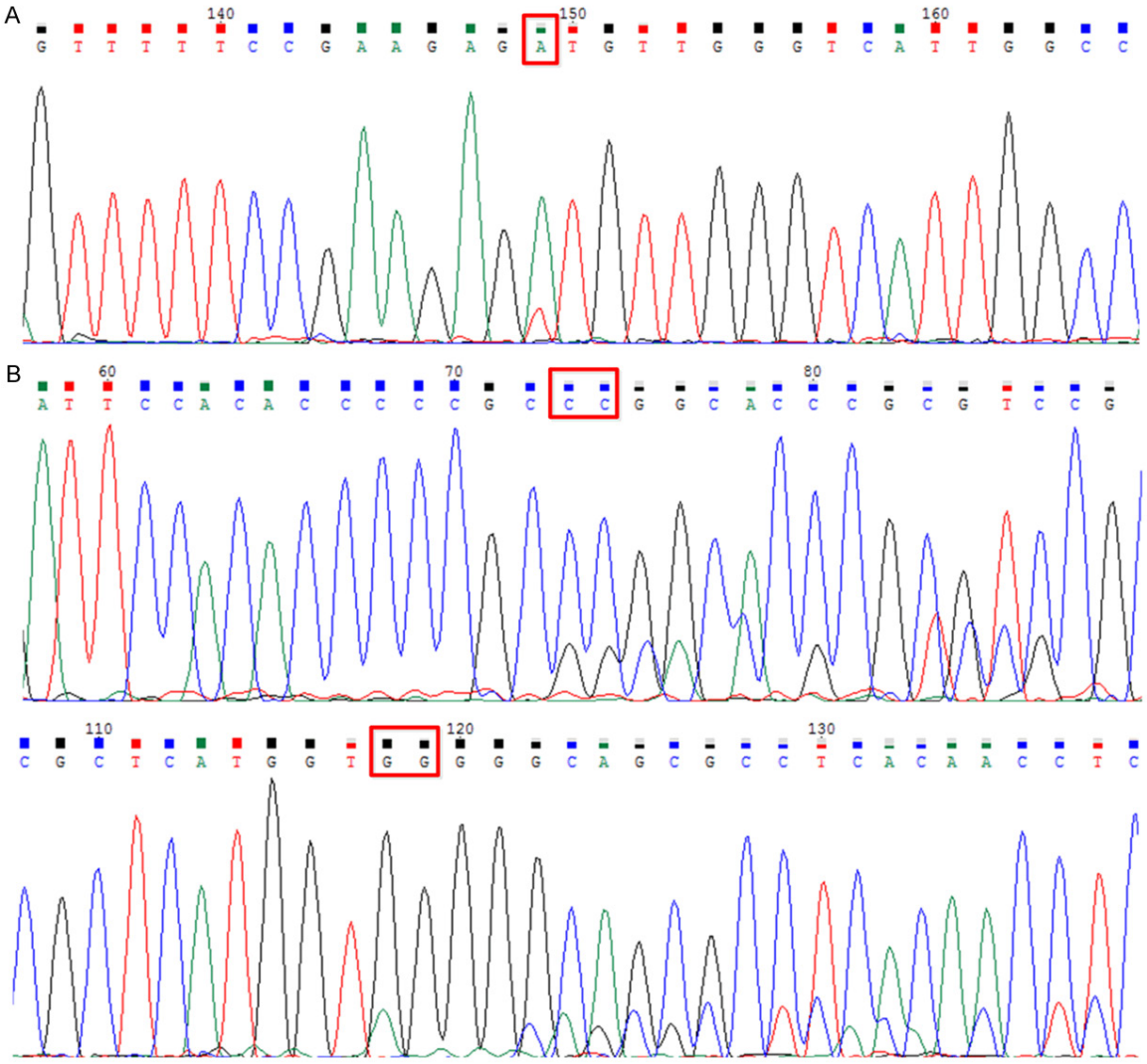

Figure 2. *mTOR* S2215T mutation (A), *TP53* P153Rfs*27 and H178Tfs*69 mutations (B) were verified by first-generation sequencing (Sanger).

sis and treatment plan, samples of the biopsied tissue were subjected to somatic variation analysis based on next-generation sequencing (NGS). NGS revealed clinically significant somatic variants, namely, the S2215T mutation in *mTOR* and *PIK3CA* amplification accompanied by *TP53* P153Rfs*27 and H178Tfs*69 mutations. *mTOR* S2215T mutation, *TP53* P153Rfs*27 and H178Tfs*69 mutations were verified by first-generation sequencing (Sanger) (**Figure 2**). Based on these genomic alterations, the patient received everolimus 10 mg qd. po. beginning on March 24, 2017. Everolimus is the 40-O-(2-hydroxyethyl) derivative of sirolimus and is an mTOR inhibitor with a pharmacological effect similar to sirolimus. Everolimus was first approved by the FDA in 2009 for the treatment of advanced renal cancer. Currently, in many clinical studies, clinicians are also use iverolimus and other mTOR inhibitors to treat other cancers with corresponding gene mutations. The patient went home and was instructed to return to the hospital every 1-2 months. The tumor was reduced based on a CT scan one month later (**Figure 1B**). The response assessment was partial response (PR) and the everolimus treatment was continuous. But the next time of the patient coming back to the clinic was four months later. During this period, he returned to the hospital on time, but refused on the grounds of good basic condition and long journey. In August, the CT scan showed new

high-density shadows in the lungs, increased bronchial stenosis and pleural effusion (**Figure 1C**). The assessment was progressive disease (PD). Subsequently in September, the CT scan showed PR (**Figure 1D**), and CT scan showed sustained response in October (**Figure 1E**) and November (**Figure 1F**). When the patient went back to the hospital for review in November, the obvious stomatitis and oral ulcer were detected, and it was suspected that this might be related to everolimus. The drug withdrawal was recommended. The patient refused any other antitumor treatment. One week after everolimus withdrawal, the patient reported improvement in oral inflammation, but the general condition of his body deteriorated by phone (details were not available). The patient died in home in December 10, 2017. The exact cause of death was unknown. The design, performance and data acquisition protocols of this study were fully in accordance with the Declaration of Helsinki. This study was approved by the Institutional Ethics Committee (IEC) of The People's Hospital of Wuzhou. An informed consent form (ICF) was signed by the patient.

Discussion

Treatment of SQCLC is dominated by traditional surgery, radiotherapy, and chemotherapy. Targeted drugs are still lacking in clinical practice, and their clinical efficacy has not been satisfactory. At present, the potential therapeutic targets and the corresponding targeted drugs for SQCLC mainly include the PI3K/AKT/mTOR pathway and its inhibitors, *EGFR* and EGFR tyrosine kinase inhibitors (TKIs), *FGFR1* and the *FGFR1* inhibitor, *DDR2* and the *DDR2* inhibitor, and insulin-like growth factor receptor 1 (*IGFR-1*) and the *IGFR-1* inhibitors. The PI3K/AKT/mTOR pathway has multiple roles in a variety of physiologic processes and is also the most frequently activated pathway during tumor development. Therefore, the PI3K/AKT/mTOR pathway is a logical therapeutic target for SQCLC. PI3K is a lipid kinase that is activated by tyrosine kinases, such as *EGFR*, and platelet-derived growth factor receptor (*PDGFR*); activated PI3K transmits phosphorylation signals downstream. *AKT* is activated and undergoes serine phosphorylation, activating the *mTOR* complex and further activating the p70S6 kinase. Throughout the process, *PTEN,* an important tumor suppressor gene, can inhibit the function of PI3K. Genome-wide sequencing identified PI3K/AKT/mTOR pathway-related gene mutations in 47% of 178 untreated SQCLC patients. The frequency of *PIK3CA* gene alterations in SQCLC is 2%-6%, most of which are gene mutations or gene amplification. S2215T is a mutation in the *mTOR* gene. It is located in the kinase domain of the protein and changes the serine at position 2215 to threonine [6]. No studies involving the function of the S2215T mutation have been reported. The S2215Y mutation at the same site is an activation mutation of the mTOR protein. The S2215F/Y mutation can significantly increase the cellular proliferation rate, and the S2215F/Y mutation has conversion potential. Therefore, it is predicted that the S2215T mutation may be a potentially carcinogenic mutation site. One patient with metastatic urothelial carcinoma carrying two *mTOR* activating mutations (E2419K and E2014K) achieved sustained complete remission for 14 months after treatment with everolimus and the multi-kinase inhibitor, pezopanib [7]. The relationship between *PIK3CA* gene mutations and the inhibitor response rate of the PI3K/Akt/mTOR signaling pathway is not conclusive. However, some clinical studies suggest that PI3K, Akt, and mTOR inhibitors may be potential therapeutic options for patients with *PIK3CA* mutations. *HER2*-positive patients with advanced breast cancer who carry *PIK3CA* activation mutations, *PTEN* deletions, and activation of the PI3K pathway may obtain progression-free survival benefits from everolimus treatment [8].

A SQCLC patient with *PIK3CA* amplification and an *mTOR* S2215T mutation, in addition to the *TP53*P153Rfs*27 and H178Tfs*69 mutations was first reported by our group. The current report is the first of an advanced SQCLC patient who underwent first-line treatment with everolimus monotherapy and showed significantly reduced posttreatment tumor volume. Specifically, the patient achieved a PR, and he had a sustained response for 10 months. This SQCLC patient with *PIK3CA* amplification and an *mTOR* mutation is the first patient who has benefited from treatment with an *mTOR* inhibitor, providing new clinical evidence supporting the use of *mTOR* inhibitors as a potential therapeutic option for SQCLC patients with abnormal activation of the PI3K/Akt/mTOR pathway.

Disclosure of conflict of interest

The authors of Jian Luo, Jinwei Hu, Aodi Wang, Guohua Shen and Ming Yao are employees of

OrigiMed. The other authors have no conflicts of interest to declare.

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