

Case Report

Treating pulmonary blastoma with EGFR tyrosine kinase inhibitor - a rare case report

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Abstract: Pulmonary blastoma (PB) is a rare primary lung malignancy, comprising 0.25-0.5% of all primary lung tumors. This article reports a 60-year-old female patient with PB, who presented progressive dyspnea with presence pleural effusion when admitted to the hospital. A mass in the right upper lung lobe was observed. The diagnosis of PB was confirmed by histological, pathological, and immunohistochemistry analyses of the biopsy samples. *EGFR* mutation (L858R in exon 21) was detected. Accordingly, an oral EGFR inhibitor, Iressa, was administered at 250 mg daily in combination with chemotherapy. The symptoms of dyspnea improved significantly, and the chest CT examination performed at 1- and 2-month after therapy showed disappearance of pleural effusion. The disease was stable according to the Response Evaluation Criteria in Solid Tumors (RECIST). The patient achieved progression-free survival (PFS) for 16 months, followed by an observation of a new mass in the right upper lung lobe. CT-guided biopsy of the new lesion was performed. The same EGFR mutation was detected; no T790M mutation or c-MET amplification was found. The second- and third-line treatments, DP (docetaxel + cisplatin) and GC (Gemcitabine + carboplatin), were provided in combination with Iressa, and pulmonary CT scan still revealed progression of the disease. The fourth-line treatment (Irinotecan, etoposide and Iressa) was provided, and chest CT showed partial remission according to the RECIST criteria. The patient achieved another 6 months of PFS. However, the patient's condition was then progressed rapidly and died due to respiratory failure at week 3 after administration of the fifth-line chemotherapy (topotecan and Iressa). The overall survival (OS) of the patient was 28 months.

Keywords: Pulmonary blastoma, progression-free survival, overall survival, EGFR

Introduction

Pulmonary blastoma (PB) is a rare aggressive neoplasm with poor prognosis, accounting for 0.25-0.5% of all primary lung tumors [1]. Pulmonary blastomas are consisted of mesenchymal and/or epithelial components resembling the fetal lung [2]. PB was first described by Barnard et al in 1952 [3]. Patients with PB are usually younger than those with small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). Apart from surgery, there are limited treatment options for PB. Although radiation and chemotherapy have been reported sporadically [4-7], there is no consensus on the standard therapy for non-resectable PB because of the rarity of the tumor type. Although molecular profiling of PB indicates that PB contains the mesenchymal and epithelial components derived from a common precursor cell line [8], the

knowledge on the underlying molecular pathology is still limited. There was a report revealing the presence of epidermal growth factor receptor (*EGFR*) in a PB case [9], but EGFR tyrosine kinase inhibitors (EGFR-TKIs) was not provided in the study. This article reports a rare case of PB with *EGFR* sensitive mutation, and provides insights on the potential use of EGFR-TKIs in the management of PB.

Case presentation

A 60-year-old Chinese woman presented progressive dyspnea starting from January 2012. The dyspnea was mild at the time of symptom onset but exacerbated when under stress. The patient had no history of fever, night sweating, wheezing, chest pain, hoarseness of voice or hemoptysis. Three months later, the patient was admitted to a local hospital and underwent

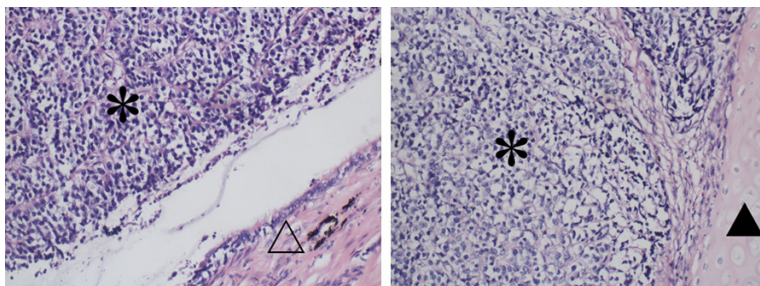


Figure 1. Microscopic findings of tumors: Diffuse growth of malignant tumor cells (*) with mesenchymal differentiation (with round to spindle-shaped nuclear and transparent cytoplasm); at the local, a small amount of normal Bronchial epithelium (Δ) and Bronchus cartilage (▲) is noted.

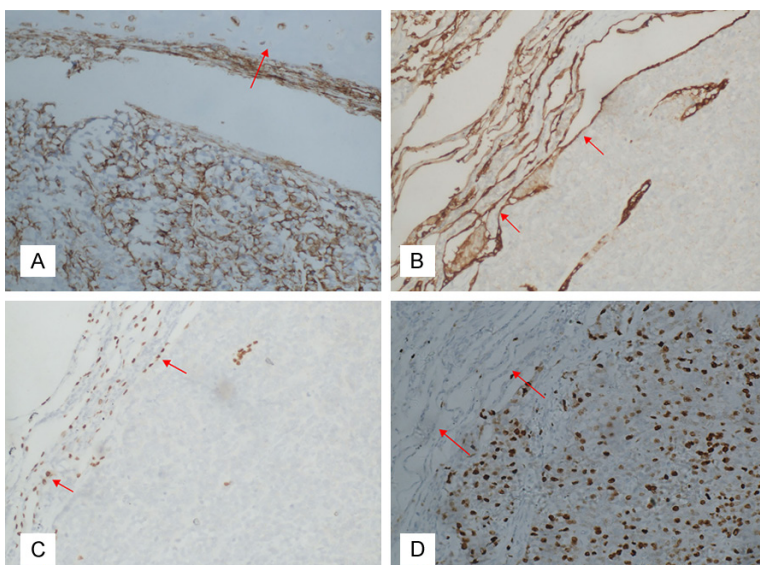


Figure 2. Immunohistochemical staining assay showed positive expression of Vimentin (A) in tumor cells and normal cartilage (as indicated by the arrows, 200X); negative expression of CK (B) and TTF-1 (C) in tumor cells, and positive expression in normal alveolar epithelium (as indicated by the arrows, 200X); expressions of Ki-67 (D) was found in > 75% of cells per field examined, indicating high cell proliferation (as indicated by the arrows, 200X).

contrast-enhanced chest CT. The CT revealed pleural effusion in the right lung and a 3.8 cm mass in the right upper lung lobe. CT-guided pleural biopsy was performed with histopathological examination. The results showed the diffuse growth of malignant tumor cells with mesenchymal differentiation in the pleural effusion. Microscopically, the tumor was composed of round to spindle-shaped immature mesenchymal cells associated with transparent cytoplasm (**Figure 1**). Immunohistochemical staining assay showed positive expression of Vimentin in tumor cells and in normal cartilage (**Figure 2A**). Furthermore, negative expression

of Creatine Kinase (CK) and Thyroid Transcription Factor 1 (TTF-1) was found in tumor cells, and positive expression was found in the normal alveolar epithelium (**Figure 2B, 2C**). Expressions of Ki-67 was found in > 75% of cells per field examined, indicating high cell proliferation (**Figure 2D**). With further pathological evaluation, diagnosis of PB in both lungs was confirmed.

Chemotherapy was suggested by oncologist, but was refused by the patient. *EGFR* mutations were tested using an amplification mutation refractory system (ARMS), and one *EGFR* mutation (L858 mutation in exon 21) was detected. An oral *EGFR*-TKI, Iressa, was administered at a daily dose of 250 mg. After 10-day treatment, the condition of dyspnea was improved significantly. Chest CT examinations performed at 1- and 2-month after admission showed disappearance of pleural effusion and the disease became stable, according to the definition in Response Evaluation Criteria in Solid Tumors (RECIST).

Representative images demonstrating the disease development during the course of

treatment were shown in **Figure 3**. In June 2013, after 16-month treatment with Iressa, a follow-up visit with chest CT demonstrated a new mass of irregular shape (approximately 3.8 × 3.4 cm) in the right upper lung lobe, adjacent to the mediastinum. In addition, there were multiple enhanced unequal-sized nodules throughout the whole right lung and linear opacities in the periphery (**Figure 3A**). The appearance of the new lesion at the right lung suggested the progression of the disease. CT-guided biopsy was performed on the new lesion in the right lung. Genetic test still showed L858 mutation in exon 21, without T790M mutation and c-MET

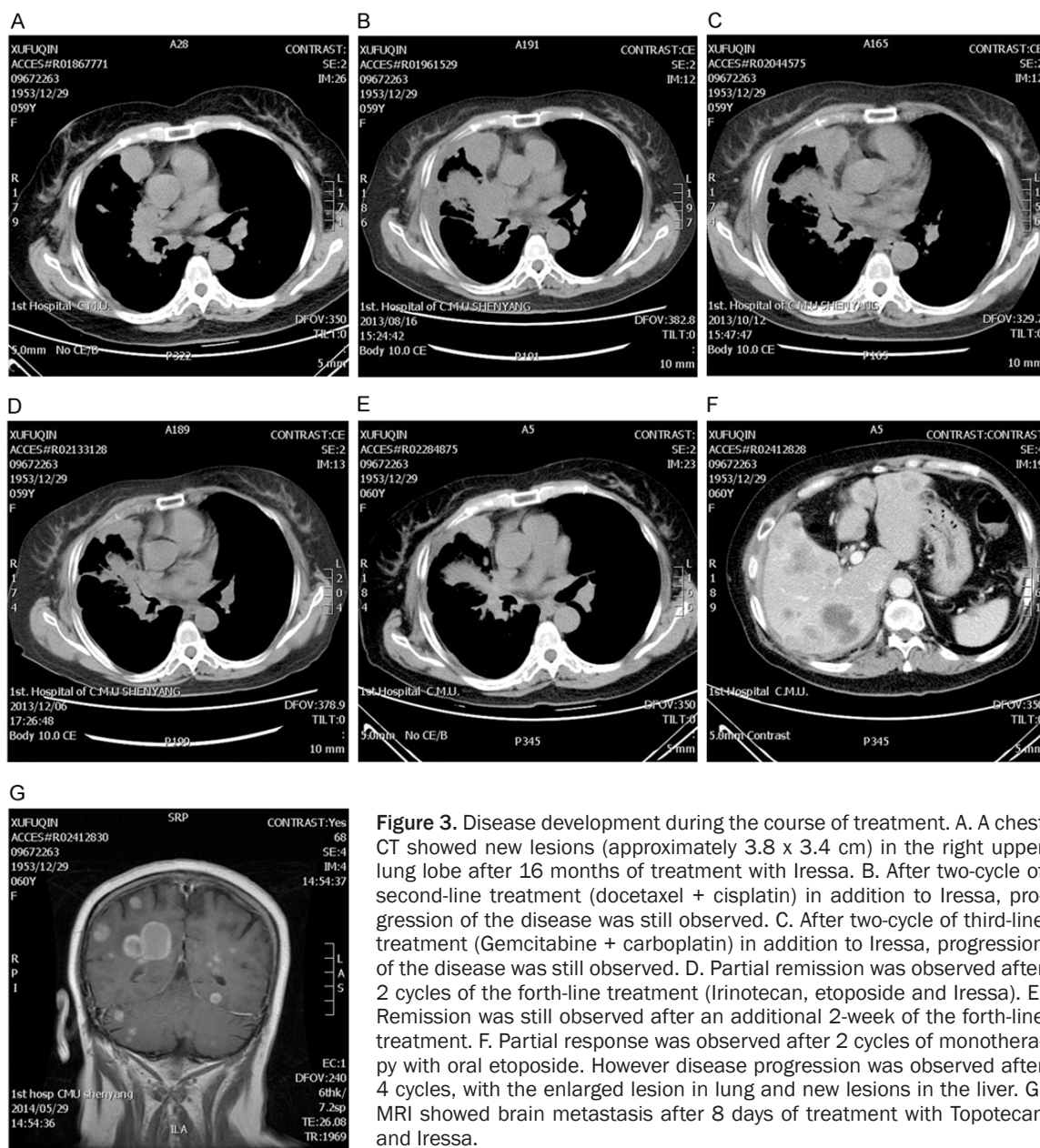


Figure 3. Disease development during the course of treatment. A. A chest CT showed new lesions (approximately 3.8 x 3.4 cm) in the right upper lung lobe after 16 months of treatment with Iressa. B. After two-cycle of second-line treatment (docetaxel + cisplatin) in addition to Iressa, progression of the disease was still observed. C. After two-cycle of third-line treatment (Gemcitabine + carboplatin) in addition to Iressa, progression of the disease was still observed. D. Partial remission was observed after 2 cycles of the fourth-line treatment (Irinotecan, etoposide and Iressa). E. Remission was still observed after an additional 2-week of the fourth-line treatment. F. Partial response was observed after 2 cycles of monotherapy with oral etoposide. However disease progression was observed after 4 cycles, with the enlarged lesion in lung and new lesions in the liver. G. MRI showed brain metastasis after 8 days of treatment with Topotecan and Iressa.

amplification. Accordingly, Iressa was administered in combination with docetaxel-cisplatin (DP) chemotherapy as the second-line treatment. Docetaxel was administered at a dose of 75mg per square meter body-surface area on the 1st day of the cycle and cisplatin at a dose of 75 mg per square meter body-surface area at a frequency of every three weeks. Oral Iressa was maintained at a dose of 250 mg daily. Contrast-enhanced chest CT after 2-cycle chemotherapy (August 2013) showed disease progression according to RECIST (Figure 3B).

Gemcitabine + carboplatin (GC) and Iressa were started as the third-line treatment. Gemcitabine was administered at 1000 mg per square meter body-surface area on the 1st and 8th day of the cycle, followed by carboplatin at a dose calculated to produce an area under the concentration time curve of 5 mg per milliliter per minute in cycles once every 3 weeks. Oral Iressa was maintained at a dose of 250 mg daily. After two cycles (October 2013), pulmonary CT scan still revealed progression of the disease (Figure 3C).

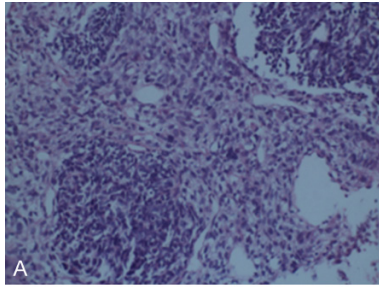
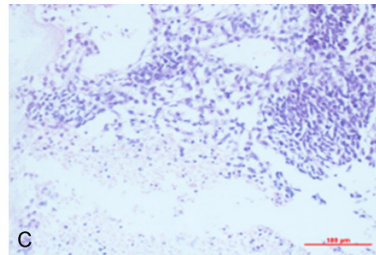
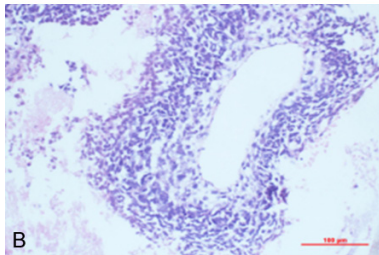


Figure 4. Microscopic H&E findings of PB: the epithelial component (A), the mesenchymal component (B), membranous localization of b-catenin (C).



Irinotecan, etoposide and Iressa were started as the fourth-line treatment. Irinotecan was administered at 65 mg per square meter body-surface area on the 1st and 8th day of the cycle, and etoposide was administered at 100 mg per square meter body-surface area on the 1st to 3rd day of the cycle, once every 3 weeks. Oral Iressa was maintained at a dose of 250 mg daily. Partial remission, according to the RECIST criteria, was observed after 2- and 4-cycle of the therapy (**Figure 3D** and **3E**). Since patients demonstrated declined physical ability and grade 3 bone marrow suppression, 4 cycles of maintenance treatment with etoposide was instituted, using oral etoposide soft capsules 100 mg per square meter body-surface area daily from the 1st to 14th day once every 3 weeks. Partial response was still observed after 2 cycles through pulmonary CT scan. However, disease progression was found after 4 cycles. Additional abdominal CT scan revealed many new lesions in the liver, indicating further progression of the disease (**Figure 3F**).

Topotecan and Iressa were started as the fifth-line treatment using topotecan at 3.5 mg per square meter body-surface area on the 1st and 8th day in the cycle once every 3 weeks. Oral Iressa was maintained at a dose of 250 mg daily. Eight days later, the patient developed severe chest tightness, shortness of breath and cough. Brain MRI, with gadolinium-diethylene-triamine pentaacetic acid in April 2014 showed brain metastasis, again indicating progression of the disease (**Figure 3G**).

As the patient refused brain radiotherapy, temozolomide and Iressa were used as the sixth-line treatment. Oral Iressa was maintained at a dose of 250 mg daily, and temozolomide was administered orally at 200 mg once every other day for five days. She died 14 days after administration of the sixth-line therapy due to respiratory failure. The overall survival (OS) of the patient was 28 months.

Discussion

Pulmonary blastoma was first described in 1952 as an 'embryoma of lung', in which the initial diagnosis was hydatid cyst [3]. In 1961, Spencer et al first used the term 'pulmonary blastoma' for this entity, in view of its resemblance with fetal tissue components. Historically, the term pulmonary blastoma had included: 1) monophasic pulmonary blastoma (MPB), also known as well-differentiated fetal adenocarcinoma (WDFAs), which has epithelial malignant components only and is regarded as a monophasic variant of PB; 2) classic biphasic pulmonary blastoma (BPB), characterized by both epithelial and mesenchymal malignant components; and 3) pleuropulmonary blastoma (PPB), a childhood tumor with features of mesenchymal malignant components only and is currently regarded as a separate entity [10]. According to the 2004 World Health Organization (WHO) classification of lung tumors, PB is classified as a subtype of sarcomatoid non-small cell lung carcinoma (NSCLC). However, the developmental origin and the correct classification of PB and carcinosarcoma remain disputable [11].

PB is different from other lung tumors with respect to the pathological features, clinical course and prognosis. More than 100 cases have been reported in the literatures, highlighting its variety in clinical manifestations. No clinical trials have been conducted to compare effectiveness of treatment regimens, because of its extreme rarity. The 1- and 5-year OS of PB is about 25% and 16% respectively [2]. Clinical characteristics such as tumor recurrence, metastasis at initial presentation, tumor

diameter > 5 cm, and lymph node metastasis are factors that indicate poor prognosis [2]. It has been shown that the prognosis of BPB is worse than that of MPB due to higher incidence of metastasis [2]. To date, there is no clear consensus about what combination therapy is optimal for the treatment of PB. Nevertheless, most researchers agree that surgical resection should be considered whenever possible [12]. The condition of the patient in this report was deemed unresectable for cure due to pleural metastasis observed. Most of the inoperable PB patients die within 12 months after diagnosis, and the present case has OS of 28 months.

Diagnosis

Approximately 25-40% patients with PB are asymptomatic. Common symptoms are cough, hemoptysis and chest pain, with pleural effusion rarely seen [2]. However, the clinical features of the patient in current report were different, with main symptoms as dyspnea and pleural effusion. Since almost all PB cases presented a unilateral large well-circumscribed solitary mass on chest radiography [10, 12], CT-guided biopsy and immunohistochemical staining are usually needed for the diagnosis of PB.

PB is a biphasic tumor in a subgroup of sarcomatoid carcinomas, which also includes subgroups such as carcinosarcoma (defined as a malignant tumor having a mixture of carcinoma- and sarcoma containing heterologous elements such as malignant cartilage, bone, or skeletal muscle) and pleomorphic carcinoma (similar tumor without heterologous elements). Both the carcinosarcoma and pleomorphic carcinoma resemble adult-type carcinoma and sarcoma histologically [10]. The morphologic structure and the expression of neuroendocrine markers are helpful in differentiating epithelial type PB from usual adenocarcinoma. PBs are composed of a mixture of epithelial and mesenchymal tissues resembling embryonic lung tissue. The epithelial components in the present case showed focal cellular atypia, mitotic figures, and branching glands composed of columnar cells with palisading elliptic nuclei and subnuclear vacuoles resembling high-grade fetal adenocarcinoma as described in carcinosarcoma (**Figure 4A**). In contrast, well-differentiated or low-grade adenocarcinoma is a typical feature of MPB. The mesenchymal components displayed a rather immature blastoma-like differentiation. The expression of

TTF-1 that was usually found in well-differentiated fetal adenocarcinoma of PB was not observed in the present case, which favored the diagnosis of carcinosarcoma (**Figure 4B**).

In addition, it was demonstrated that low-grade WDFAs constantly showed aberrant nuclear or cytoplasmic localization of β -catenin, while high-grade WDFAs showed the same membranous localization of β -catenin as conventional pulmonary adenocarcinoma, which was also observed in the present case (**Figure 4C**). The adult type PB is a rarely seen biphasic tumor. It contains a primitive epithelial component and a primitive mesenchymal stroma that looks like WDFAs. The adult type PB is a highly invasive intrathoracic neoplasm and mainly found in adults with an unfavorable prognostic outcome. The developmental origin of both tumor components is unclear and an origin from two or more stem cells (multiclonal hypothesis) or an origin from a single stem cell that differentiates into separated epithelial and mesenchymal directions (monoclonal hypothesis) seems possible.

Treatment

Surgical resection, such as lobectomy and dissection of diaphragm lymph nodes, is the preferred treatment option for PB. The role of chemotherapy during late-stage PB or in adjuvant is not well defined, but chemotherapy is considered a feasible option.

Various combination chemotherapies have been reported for treating PB [4-7], but there is no consensus or standard treatment guideline on chemotherapies. Since EGFR mutation is identified in the current case, targeted therapy EGFR-TKI was provided to the patient. EGFR is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. EGFR mutations are most commonly found in patients with NSCLC. The prevalence of EGFR mutations in adenocarcinomas is about 10% in Caucasian and more than 50% in Asian populations [13]. The Iressa Pan-Asia Study (IPASS) reported that the objective response rate was 71.2% with gefitinib versus 47.3% with carboplatin-paclitaxel in the mutation-positive subgroup [14]. Accordingly, the latest 2015 NCCN guidelines recommend analyzing EGFR mutations before the use of the targeted therapy. EGFR-TKIs are recognized as a standard first-line therapy for patients with activating EGFR mutations. There was a study

reported an *EGFR* mutation in one of their five PB cases, suggesting *EGFR* mutation may also occur in PB [9]. However, EGFR-TKIs were not used in the reported case. In our case, EGFR-TKI was used as treatment after confirmation of *EGFR* mutation, and PFS of the patient was as long as 12 months. Although, it is difficult to assess the efficacy of EGFR-TKIs in the treatment of PB because of the lack of control, this is the first report that shows the benefit of using EGFR-TKI in PB patients with positive EGFR mutation.

Since the patient failed to respond to Iressa, the third-generation platinum-based chemotherapy agents were used as the second- and third-line treatment. However, the therapeutic effect was not good and the patient's condition progressed rapidly. Considering the PB was histologically similar with a neuroendocrine tumor in the current case, we then used a chemotherapy regimen that is sensitive to neuroendocrine tumors as the fourth-line chemotherapy. As a result, the patient achieved optimal PR and a PFS as long as 7 months.

Based on the experiences in the present case, we would like to provide some suggestions on the treatment of PB. In cases with positive *EGFR* mutations, EGFR-TKIs can be chosen as the first-line therapy, and genetic re-testing is recommended upon disease progression to determine potential of drug resistance. Depending on the pathohistologic features, chemotherapy regimens indicated for other cancers could also be considered as a treatment for PB.

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