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Gefitinib improves severe bronchorrhea and prolongs the survival of a patient with lung invasive mucinous adenocarcinoma: A case report

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Abstract

BACKGROUND

Lung invasive mucinous adenocarcinoma (LIMA), formerly referred to as mucinous bronchioloalveolar carcinoma (BAC), is a rare disease that usually presents as bilateral lung infiltration, is unsuitable for surgery and radiotherapy, and shows poor response to conventional chemotherapy.

CASE SUMMARY

We report a 56-year-old Chinese man with a history of smoking and epidermal growth factor receptor (EGFR) mutation-positivity who was initially misdiagnosed as severe pneumonia, but was ultimately diagnosed as a case of invasive mucinous adenocarcinoma of the lung by CT-guided percutaneous lung biopsy. Bronchorrhea and dyspnea were improved within 24 h after initiation of gefitinib therapy and the radiographic signs of bilateral lung consolidation showed visible improvement within 30 days. After more than 11 months of treatment, there is no evidence of recurrence or severe adverse events.

CONCLUSION

Although the precise mechanism of the antitumor effects of gefitinib are not clear, our experience indicates an important role of the drug in LIMA and provides a reference for the diagnosis and treatment of this disease.

⁹ **INTRODUCTION**

Lung cancer is the second most common cancer worldwide and the leading cause of cancer-related deaths, accounting for almost one-quarter of all cancer-related deaths^[1]. Non-small cell lung cancer (NSCLC) is the main pathological type of lung cancer, accounting for about 80%–85% of all cases of lung cancer^[2, 3]. In the 2015 World Health Organization (WHO) classification of lung tumors, lung invasive mucinous adenocarcinoma (LIMA) is classified as a variant of invasive lung adenocarcinoma, which accounts for approximately 5%–10% of lung adenocarcinomas^[4]. The diagnostic hallmark of IMA is tall columnar cell morphology with abundant intracellular/extracellular mucus and invasive adenocarcinoma patterns (such as acinar, lepidic, papillary, and predominant patterns)^[5]. The clinical presentation of LIMA is different from that of other subtypes of adenocarcinoma. LIMA typically shows diffuse lung involvement, which results in severe respiratory symptoms, such as bronchorrhea and dyspnea^[6, 7]. In addition, LIMA also tends to be resistant to conventional chemotherapy, and patients typically have a short survival time after detection of the cancer^[8].

Recent years have witnessed important breakthroughs in the treatment of NSCLC, which has evolved from traditional surgery, chemotherapy, and radiotherapy to the era of molecular targeted therapy and immunotherapy. The development of epidermal growth factor receptor (EGFR) targeted tyrosine kinase inhibitors (TKIs) have helped facilitate the concept of personalized cancer therapy into a reality^[9]. Several studies have demonstrated high antitumor activity of EGFR-TKIs against BAC and the therapeutic response can be dramatic and long-lasting^[10, 11]. Gefitinib is a reversible EGFR targeted TKI that competes for Mg-ATP binding sites in the EGFR catalytic

region, thereby blocking signaling, inhibiting cancer cell proliferation, and inhibiting mitogen-activated protein kinase activation, inducing cancer cell apoptosis^[12].

Here, we report a patient with LIMA who was successfully treated with gefitinib. ¹ Bronchorrhea and dyspnea were improved within 24 h after treatment with gefitinib, and ⁴ the radiographic signs of bilateral lung consolidation were visibly improved within 30 days. As of 11 mo after initiation of gefitinib, there are no signs of tumor progression.

CASE PRESENTATION

Chief complaints

On October 29, 2021, a 53-year-old man presented to the department of respiratory medicine at our hospital due to shortness of breath and excessive sputum production for 3 mo.

History of present illness

As shown in Figure 1, the patient expectorated large amount of white and foamy sputum (approximately 700 mL/day), accompanied by chest tightness and shortness of breath. He was earlier treated with oral amoxicillin and expectorants, but the results were not satisfactory.

History of past illness

The patient had no prior chronic disease, but had recently lost 2 kg of his body weight.

Personal and family history

He was a chronic smoker (20 cigarettes per day for more than 10 years). ³ The patient denied having a family history of lung cancer, hypertension, or coronary heart disease.

Physical examination

Vital signs at admission were as follows: body ¹² temperature, 37.8°C; heart rate, 114/min; respiratory rate, 30/min; blood pressure, 147/110 mmHg; oxygen saturation, 90%

(under nasal cannula 5 L/min oxygen inhalation). Physical examination revealed coarse crackles in both lungs.

Laboratory examinations

¹¹ Blood gas analysis showed respiratory failure with an oxygen partial pressure (PaO₂) of 54 mmHg and oxygenation index of 129 mmHg. Conventional inflammation markers (C-reactive protein: 1.37 mg/mL [reference range, 0–10], procalcitonin: 0.05 ng/mL [<0.05], white blood cell count: $10.9 \times 10^9/L$ [$4\text{--}10 \times 10^9$], absolute neutrophil count: $6.35 \times 10^9/L$ [$1.8\text{--}6.3 \times 10^9$], and neutrophil percentage: 58.3% [40–75%]) were measured on the day of clinical examination. No obvious abnormalities were found in coagulation, sputum smear microscopy, sputum culture, tuberculosis bacilli gamma interferon release test, rheumatoid factor, liver and kidney function, tumor markers (carcinoembryonic antigen, cytokeratin, neuron-specific enolase), connective tissue related antibodies, or anti-neutrophil cytoplasmic antibody.

Imaging examinations

Chest high-resolution computed tomography (HRCT) scan showed large flaky hyperintense shadows in both lungs, especially in the right lung (Figure 2).

FINAL DIAGNOSIS

The clinical picture was suggestive of infectious pneumonia and he was administered routine anti-infection, expectorant, and antispasmodic treatment. However, the patient showed no symptomatic improvement after 3 days of treatment. Bronchoscopy was performed to further clarify the cause, which showed a lot of white secretions in the trachea (Figure 3). The right lower lobe was lavaged and sent for next-generation sequencing (NGS). However, NGS results showed no pathogens. Repeat chest CT performed on the 7th day of treatment showed an increase in the lung solid lesions compared with those on admission, while there was no significant change in inflammatory marker levels. Subsequently, the patient underwent CT-guided

percutaneous lung biopsy, which confirmed the diagnosis of LIMA (Figure 4). In addition, the tissue specimen was subjected to *EGFR* analysis. Systematic investigations revealed no metastases other than the lungs, and based on clinical and histological findings, the patient was diagnosed with stage IV disease. Fortunately, genetic testing revealed positive *EGFR*-21 mutation (c.2573T > G : p.L858R).

TREATMENT

Other medications were discontinued, and treatment with an *EGFR*-tyrosine kinase inhibitor, gefitinib (250 mg/d) was commenced.

OUTCOME AND FOLLOW-UP

Twenty-four hours after initiation of treatment, the patient showed remarkable improvement in symptoms with alleviation of dyspnea and bronchorrhea. ¹ Arterial blood gas analysis showed a PaO₂ of 81 mmHg and oxygenation index of 279 mmHg upon nasal inhalation of 2 L/min O₂. The volume of sputum discharged decreased from 700 to 300 mL/day, and 3 days later it was further reduced to 100 mL/day. Chest CT scan showed remarkable improvement of infiltration 30 days (Figure 2) after treatment. After more than 11 months of treatment (Figure 2), there was no evidence of recurrence or severe adverse events.

DISCUSSION

Adenocarcinoma is the most commonly diagnosed pathological subtype of NSCLC. LIMA was recognized as a distinct subtype of lung adenocarcinoma with unique biological properties, as well as a different prognosis compared with other lung adenocarcinoma subtypes ^[13]. Previous studies have shown that LIMA may originate from type II alveolar epithelial or Clara cell metaplastic lesions, and further develop atypical hyperplasia and carcinogenesis^[14, 15]. ² Tumor cells in IMAs are highly discrete, and show poor adhesion; These easily diffuse widely through alveolar pores and small airways, which is an important reason for their diffuse distribution^[16, 17]. In a study by

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Cha *et al*, 13.9% of IMAs were initially identified as pneumonia, which is much higher than the rate of initial misdiagnosis of invasive non-mucinous adenocarcinomas as pneumonia^[18]. Watanabe *et al* analyzed the data of 40 patients with mucinous adenocarcinoma who underwent surgical resection; they found that 25% patients showed either pneumonia-like consolidation or multifocal patchy consolidation on chest CT^[19]. Invasive mucinous adenocarcinoma and pneumonia are not easy to distinguish due to the large overlap of clinical features, including cough and sputum symptoms^[20].

This was also an important reason why this case was initially misdiagnosed as pneumonia. For middle-aged and elderly patients, those with pulmonary infiltrates that are not absorbed by anti-infection treatment, and who continue to experience cough with expectoration of large amount of white sputum, the possibility of pneumonia-type lung cancer should be considered and a pathological diagnosis obtained. Pathology is still the gold-standard for the diagnosis of the disease, and the accurate diagnosis of LIMA is a key imperative to initiate appropriate treatment and improve the prognosis.

Advances in the field of molecular profiling and targeted therapies have brought about a paradigm shift in the treatment landscape for NSCLC^[21]. Lung adenocarcinoma patients with genetic mutations can achieve prolonged survival with corresponding targeted therapy. According to previous studies reporting gene mutation analysis in the context of LIMA, KRAs are the most common mutation type accounting for approximately 35%–75%, while the incidence of Tp53 mutation is approximately 46%; the incidence of *EGFR* mutation, *ALK* rearrangement, and *BRAF* mutation is very low^[22-24]. However, several studies have demonstrated high antitumor activity of EGFR-TKIs against LIMA, and the therapeutic response can be dramatic and long-lasting. In 2013, Lopez-Gonzalez *et al* described a 66-year-old woman diagnosed with right lung IMA who tested positive for *EGFR* mutation; treatment with gefitinib led to significant shrinkage of lesions, and the patient showed a long progression-free survival^[25]. Moreover, Pastorino *et al* claimed that long-term gefitinib therapy may be effective in the management of atypical adenomatous hyperplasia (AAH) and multifocal IMA

presenting as diffuse ground glass opacities (GGO), when fluorescence in situ hybridization or molecular testing are indicative of sensitivity^[26].

Our patient was *EGFR* mutation-positive for which the recommended treatment is gefitinib. This treatment resulted in a rapid reduction of bronchorrhea, associated with a dramatic improvement in dyspnea, hypoxia, and radiographic abnormalities. Gefitinib is an orally-active, selective *EGFR*-TKI that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells^[27]. Of note, some studies have reported contradictory findings about LIMA without *EGFR* mutation treated with gefitinib^[28, 29].

CONCLUSION

At present, the exact mechanism of action of targeted drugs for tumors is not fully understood. Owing to the low number of patients treated with these drugs, further research and follow-up studies are required to obtain more definitive evidence.

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SIMILARITY INDEX

PRIMARY SOURCES

1 Takeshi Kitazaki, Masaaki Fukuda, Hiroshi Soda, Shigeru Kohno. "Novel effects of gefitinib on mucin production in bronchioloalveolar carcinoma; two case reports", Lung Cancer, 2005 70 words — 4%
Crossref

2 www.ncbi.nlm.nih.gov 70 words — 4%
Internet

3 www.wjgnet.com 36 words — 2%
Internet

4 Seiji Yano. "A report of two bronchioloalveolar carcinoma cases which were rapidly improved by treatment with the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 ((quote)Iressa(quote)1", Cancer Science, 5/2003 32 words — 2%
Crossref

5 Ugo Pastorino. "Prolonged Remission of Disseminated Atypical Adenomatous Hyperplasia Under Gefitinib", Journal of Thoracic Oncology, 02/2009 25 words — 1%
Crossref

6 oaji.net 25 words — 1%
Internet

-
- 7 Seiji Yano. "Molecular mechanisms of angiogenesis in non-small cell lung cancer, and therapeutics targeting related molecules", Cancer Science, 6/2003
Crossref 22 words — 1%
-
- 8 academic.oup.com
Internet 22 words — 1%
-
- 9 mdpi-res.com
Internet 19 words — 1%
-
- 10 Greg V. Manson, Patrick C. Ma. "Response to Pemetrexed Chemotherapy in Lung Adenocarcinoma-Bronchioloalveolar Carcinoma Insensitive to Erlotinib", Clinical Lung Cancer, 2010
Crossref 18 words — 1%
-
- 11 Fang He, Hai-ying Gong, Guo-lu Jiang, Xiao-ju Chen, Qian-jing Yao, Li Jiang. "Diffuse panbronchiolitis: A case report from a Chinese consanguineous marriage family and literature review", Chronic Respiratory Disease, 2020
Crossref 17 words — 1%
-
- 12 W S Lim. "Pandemic flu: clinical management of patients with an influenza-like illness during an influenza pandemic", Thorax, 2007
Crossref 16 words — 1%
-
- 13 Yoon Jin Cha, Hye Ryun Kim, Hye-Jeong Lee, Byoung Chul Cho, Hyo Sup Shim. "Clinical course of stage IV invasive mucinous adenocarcinoma of the lung", Lung Cancer, 2016
Crossref 16 words — 1%
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