CASE REPORT

http://dx.doi.org/10.4046/trd.2014.77.6.271
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2014;77:271-273

TRD
Tuberculosis and Respiratory Diseases

Systemic Nocardiosis Mimicking Disease Flare-up after Discontinuation of Gefitinib in a Patient with *EGFR*-Mutant Lung Cancer

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Disease flare-up after discontinuing epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) has been considered as a critical issue in lung cancer patients who have experienced radiologic progression after showing initial durable response. This is a case of systemic nocardiosis that occurred after chronic steroid use for radionecrosis from stereotactic radiosurgery. It was initially thought as a disease flare-up after stopping EGFR-TKI.

Keywords: EGFR Tyrosine Kinase Inhibitor 324674; Nocardia Infections; Carcinoma, Non-Small-Cell Lung; Radiosurgery

Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) tend to be dramatically effective in some patients with non-small cell lung cancer harboring sensitizing *EGFR* mutations[1]. However, most of the patients with *EGFR*-mutant lung cancer who have initially shown durable response to EGFR-TKI eventually acquire resistance to the drug. Moreover, a few of them experience accelerated progression of disease on discontinuation of EGFR-TKI[2]. Thus, even after radiologic progression, maintenance of EGFR-TKI until administration of another effective treatment is clinically recommended in this patient group. We report a case of systemic nocardiosis occurring after chronic steroid use for radionecrosis from stereotactic radiosurgery (SRS), which initially was confused as a disease flare-up after stopping EGFR-TKI.

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Received: Jun. 13, 2014
Revised: Jul. 28, 2014
Accepted: Sep. 3, 2014

Case Report

A 56-year-old man underwent left lower lobe lobectomy for lung adenocarcinoma (T2N2M0) in 2007, and was found to have recurrent lung cancer in the lung, brain, and left adrenal gland in 2009. He was treated with 15 cycles of gemcitabine plus navelbine from November 2009 to December 2010, and then six cycles of pemetrexed from March 2011 to June 2011. After progression in the lung, gefitinib 250 mg was started in July 2011 since *EGFR* exon 19 deletion mutation was detected in his primary tumor.

The patient had dragged his right leg since May 2011, and the motor weakness progressively worsened for one year on gefitinib despite stable disease status of the lung and brain, from grade 5 to grade 3 on manual muscle testing. He underwent SRS of 30 Gy for the left frontal brain metastasis during the 11th cycle of gefitinib from May 31, to June 4, 2012. However, he suffered from recurrent right hemiparesis from July 2012, and findings from perfusion magnetic resonance imaging (MRI) and positron emission tomography of the brain favored radiation necrosis with peritumoral edema over disease

progression. He thus continued to take low-dose dexamethasone together with gefitinib for 3 months until September 4, 2012, when computed tomography (CT) scan after 15th cycle suggested progressive disease in the lung and gefitinib was discontinued.

Two weeks later, he presented with intermittent fever, chill, and productive cough on September 21, 2012. A physical examination was notable for coarse crackles in the left lung field. A blood test showed white blood cell count of $13\times10^3/\mu L$ (segmented neutrophils, 88.6%; lymphocytes, 5.4%), and C-reactive protein of 20.0 mg/dL. A chest X-ray revealed increase in the size of left hilar mass and multiple right lung nodules compared to that taken two weeks before (Figure 1).

Rapidly growing lung lesions in the context of lung cancer recently coming off EGFR inhibitor put reactivation of *EGFR*-mutant lung cancer high on our differential list, while other inflammatory conditions such as pneumonia remained to be ruled out. A bronchoscopy was subsequently performed, which revealed whitish mucosal lesion in the left upper bronchial stump with bronchitis in the left lower basal trunk. Biopsy from the bronchus showed chronic active inflammation, but culture grew no bacteria.

Accordingly, empirical piperacillin plus tazobactam was administered for 10 days, and gefitinib was resumed for three weeks, and another round of restaging was conducted on October 11, 2012. Chest CT showed marked increase in multiple pulmonary nodules, while new multi-septated necrotic enhancing brain lesions were noted on brain MRI. A new brain lesion in the left frontal lobe was confirmed as an abscess by stereotactic biopsy. Additionally, a sputum culture collected on September 19, 2012, at the time of his admission, grew non-tuberculous acid-fast organisms, which was identified 3 weeks later as *Nocardia* species through 16S rRNA polymerase chain reaction and direct sequencing.

He was started on parenteral trimethoprim-sulfamethoxazole on October 15 for systemic nocardiosis and his fever abated two days after starting the drug with gradual improvement in chest X-ray. Six weeks later, chest CT showed

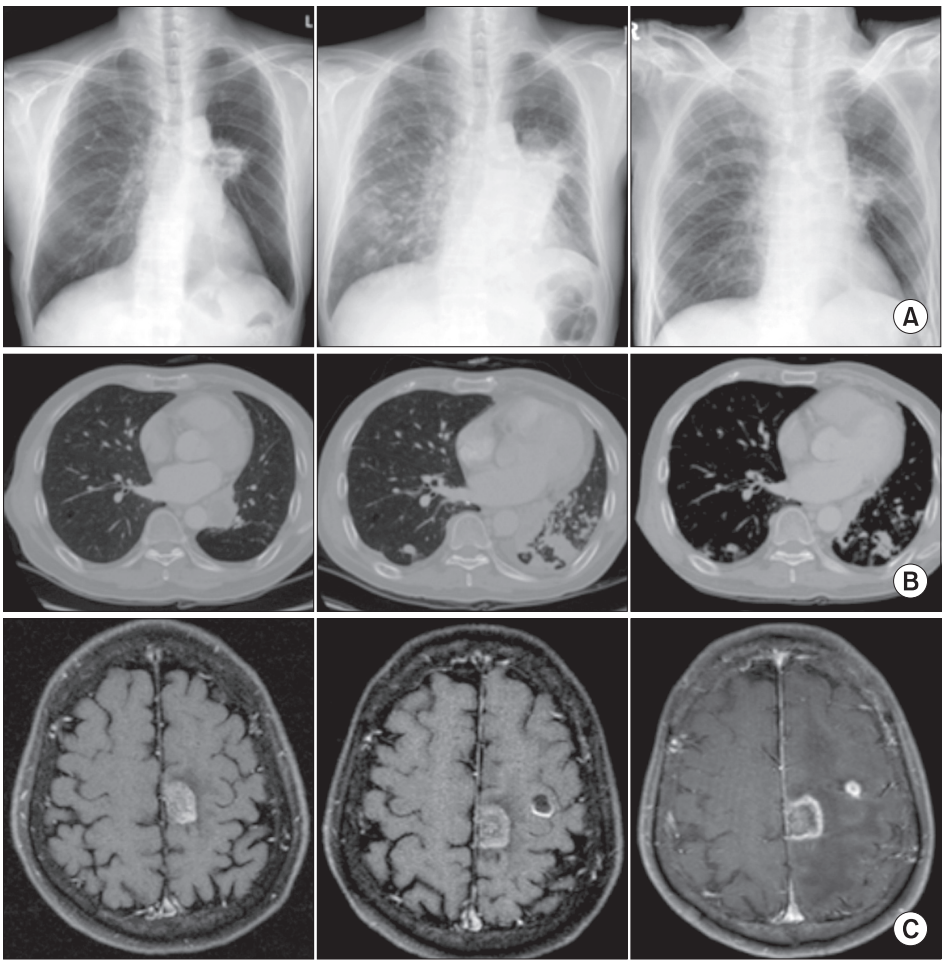

Figure 1. Serial radiologic evaluation including chest X-ray scans (A) and brain magnetic resonance imaging (B, C). TMP-SMX: trimethoprim-sulfamethoxazole.

decreased multiple pulmonary nodules in number and size. Brain MRI on November 30, 2012 showed multiple enhancing brain lesions decreased in size with peripheral thick enhancement, which suggested chronic stage of brain abscess.

Discussion

We report a case in which a tumor flare-up was initially suggested occurring shortly after discontinuation of the gefitinib, but turned out to be disseminated nocardiosis. In this case, systemic infection overlapped with known cancer lesions, resembling cancer progression on the imaging, and rarity of this opportunistic infection, as well as lack of pathognomonic sign and sensitive diagnostic tool for it might as well contributed to the initial confusion.

Nocardiosis is most common in immune-compromised patients with predisposing conditions being chronic lung disease, diabetes mellitus, hematologic and other malignancies, transplantation, acquired immune deficiency syndrome, and chronic steroid use[3,4]. It usually affects the lungs and involves other sites of the body through hematogenous dissemination. It has a high morbidity and mortality rate, which ranges from 7% to 44% for disseminated nocardiosis[4]. In this case, prolonged steroid therapy, which was required to control symptomatic cerebral necrosis after SRS, contributed to development of such an opportunistic infection. Although SRS has become an increasingly popular therapeutic tool for patients with metastatic brain lesions, which delivers single high dose of radiation precisely focused at intracranial targets, it is associated with symptomatic cerebral necrosis in 2%–10% of cases[5,6]. Neurological deficits associated with brain necrosis frequently respond to corticosteroid, but this also entails adverse effects from steroid, including deficient host immunity, as in our patient.

Accelerated disease progression after TKI discontinuation is a visible threat for patients with *EGFR*-mutant lung cancer, which has acquired resistance to the drug. Chaft et al.[2] defined disease flare of *EGFR*-mutant lung cancer as hospitalization or death attributable to cancer progression during the washout period after TKI in their study, and reported its occurrence rate as 23%. Important differential diagnosis in such cases includes infectious complications, as both can lead to rapid clinical deterioration, but differ in therapeutic approach. Confirmative evaluation such as percutaneous biopsy might be of help to guide further management in appropriate clinical setting.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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