

Quick regression of brain metastases from lung adenocarcinoma with epidermal growth factor receptor-tyrosine kinase inhibitor treatment: A case report and literature review

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Abstract. Brain metastasis (BM) commonly occurs in patients with advanced lung cancer, and is associated with poor prognosis and limited treatment options, particularly for end-stage patients who are in poor physical and mental state. We herein present a case of lung adenocarcinoma with BM, as revealed by tumor marker and imaging studies. The patient was a 74-year-old woman who was diagnosed with lung adenocarcinoma with several metastatic lesions in the mediastinal lymph nodes, bone and brain. The patient underwent two cycles of chemotherapy, but the cancer recurred with enlarged BM, resulting in confusion and body dysfunction. The patient then received epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy with icotinib. After approximately 12 h of treatment the symptoms disappeared, and the metastatic lesions in the brain largely regressed in the following months. Our case indicates that the EGFR-TKI icotinib may provide a rapid and safe approach for emergency situations with BM from lung adenocarcinoma.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide (1). Brain metastasis (BM) is a common secondary localization of the disease in lung cancer patients, encountered in ~7.4% of non-small-cell lung cancer (NSCLC) cases at diagnosis (2), and 25-30% of the cases over the course of the disease (3). The prognosis of NSCLC with BM is poor

and the mortality is high (4,5). The most common treatment for these patients is radiation therapy (6,7); however, the therapeutic options are limited in an emergency setting, as well as for end-stage patients. In this report, we present the case of a NSCLC patient with BM who received epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy, with quick regression of the symptoms. The present case suggests that EGFR-TKI therapy may be effective for late-stage NSCLC patients, or in an emergency setting.

Case report

On, November 19, 2013, a 74-year-old female patient was admitted to the Respiratory Department of The Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) complaining of persistent cough and progressive dyspnea. The patient had already undergone a lung computed tomography (CT) scan at a local hospital, which revealed a mass in the lower lobe of the left lung, combined with left pleural effusion and mediastinal lymph node enlargement. Following admission, a contrast-enhanced CT revealed a mass sized ~98x79 mm, blocking the left main bronchus and invading the left pulmonary artery and its branches. Bronchoscopy was performed and a tumor was identified in the left lower airway. Pathological examination of a biopsy specimen identified the lesion as lung adenocarcinoma. Genetic analysis identified an exon 19 EGFR mutation in the patient. Following magnetic resonance imaging and ultrasound studies, metastases were found in the brain, skull, adrenal gland and abdominal lymph nodes. No significant symptoms or body dysfunction were associated with the metastases, except for a painless horn-like protrusion on the right side of the forehead. Administration of EGFR-TKI therapy was immediately recommended. However, the patient's family rejected this treatment strategy due to its high cost, and opted for chemotherapy instead. Pemetrexed disodium (75 mg/m²) and carboplatin (area under the curve = 5) were administered every 21 days for a total of two cycles.

Eleven days after the second cycle of chemotherapy, the patient was admitted to our hospital due to left body dysfunction for 5 days. The physical examination revealed no changes in muscle tone. Muscle strength was rated 0/5 in the left upper

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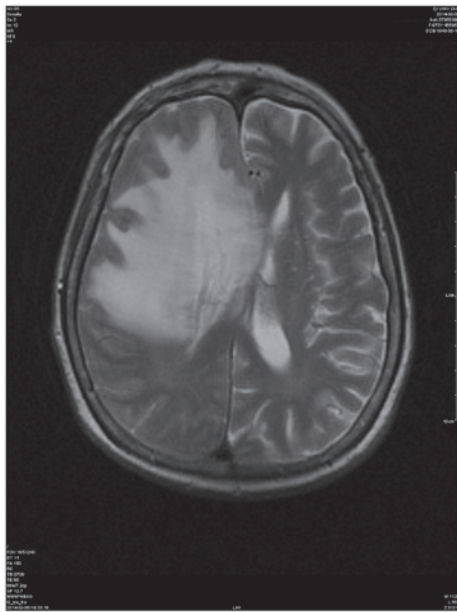


Figure 1. Contrast-enhanced magnetic resonance imaging prior to epidermal growth factor receptor-tyrosine kinase inhibitor treatment, showing brain metastases destroying the frontoparietal bone plate and diploe. The right anterior horn of the lateral ventricle appears compressed and the midline is shifted to the left.

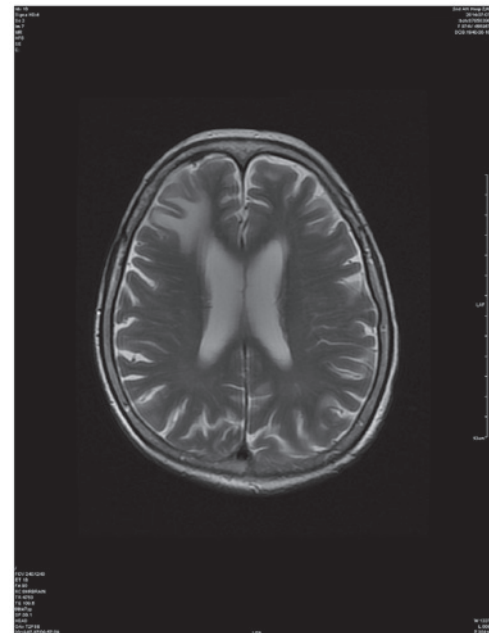


Figure 2. Contrast-enhanced magnetic resonance imaging after 4 months of epidermal growth factor receptor-tyrosine kinase inhibitor treatment, showing substantial regression of the metastatic lesion.

limb and 1/5 in the left lower limb. The right-sided muscle strength was 5/5. The right patellar tendon reflex was rated as 2+, but was absent on the left side. The Babinski sign was negative. The patient underwent an emergency brain MRI scan, which revealed that the brain metastatic lesion had grown significantly compared with the original scan. Contrast-enhanced MRI showed T1 and T2 hyperintense changes in the superior frontal gyrus, as well as enhancement in the nodular zones of the meninges surrounded with cerebral edema, destruction of the frontoparietal bone plate and diploe. The right anterior horn of the lateral ventricle was compressed and the midline was shifted to the left. Imaging diagnoses included frontal bone malignancy with involvement of the superior frontal gyrus, which was considered as metastasis (Fig. 1).

D-glycerol and steroids were initially administered, but this treatment was ineffective. Moreover, brain surgery was strongly recommended to avoid cerebral herniation; however, the patient's family rejected surgical intervention. Administration of the EGFR-TKI icotinib (125 mg, p.o. 3 times/day) was then recommended, to which the family agreed. Surprisingly, the patient's left body function progressively improved after taking 4 tablets. The physical examination revealed that the muscle strength of the left upper limb was 2/5 and of the left lower limb 3/5. The Babinski sign was negative. After 48 h, the left body dysfunction had resolved. In addition, the dimensions of the horn-like lesion on the patient's forehead markedly decreased, from 18.3x2.3 to 12.2x1.5 cm. After 4 days of observation, the patient was discharged.

Over 4 months later, the patient underwent a follow-up brain MRI scan, which revealed that the metastatic lesion was significantly smaller compared with prior to treatment (Fig. 2). In October, 2014, the patient remained alive and was continuing icotinib therapy, without other chemotherapies.

Discussion

Approximately 20-40% of NSCLC patients develop BM, which is associated with a poor prognosis. The majority of these patients survive for 3-6 months and the 1-year survival rate is 10% (4,8,9). Considerable efforts have been made to explore additional or alternative treatment modalities to improve survival, quality of life and local tumor control.

For patients with a single metastatic lesion in the brain, whole-brain radiation therapy (WBRT) is the standard of care, and is often combined with chemotherapy or surgery. When combined with surgical resection, WBRT reduces the risk of relapse and may increase the overall survival of patients with BM (5,10). Moreover, the combined treatment of pemetrexed-cisplatin with concurrent WBRT has been proven effective in patients with NSCLC and BM (11). However, these treatment protocols require the patients to be in relatively good health (i.e., high Karnofsky performance status score) prior to treatment. If a patient is in poor health, as is common with advanced NSCLC, fewer treatment options are available.

In the present case, the patient had a large metastatic lesion in the brain, which invaded the skull in the area of the forehead and caused a midline shift, potentially increasing the risk of increased intracranial pressure (IICP). Glycerol and steroid therapy was not effective in this patient. Given the patient's severe conscious impairment and increasing IICP, she was in an emergency situation requiring a rapid response. Ideally, local control of tumor progression by surgical removal, with or without radiation or radiosurgery, may be the first or optimal method to manage IICP, as illustrated by a previous case of a 57-year-old female patient with a large BM who was successfully treated with macroscopically complete excision of the brain tumor and postoperative radiotherapy (12). However, in our case, our patient had a poor baseline performance

status, she was elderly, and the large lung tumor caused left lung atelectasis and invaded the left pulmonary artery, which further increased the risk associated with anesthesia and surgery. Second, edema and brain injury following surgery or radiotherapy is highly possible, potentially compromising the patient's quality of life. The primary tumor in the lung was not sensitive to radiotherapy; therefore surgery and WBRT were not considered to be a safe and effective option for this patient.

As an alternative to WBRT, other therapeutic approaches are available to treat BM. Drugs targeting mutated EGFR and anaplastic lymphoma kinase (ALK) genes have been highly effective when administered systemically (13,14). Several reports demonstrated that gefitinib or icotinib are associated with a favorable response in lung adenocarcinoma with BM, particularly in cases harboring EGFR mutations, such as our patient (15-19). EGFR-TKIs are reported to cross the blood-brain barrier, although it has been suggested that TKI concentration is reduced in the central nervous system compared with the serum levels (20). In such cases, increased doses may improve the efficacy (21). However, in the present case, the standard dose of icotinib quickly relieved the patient's symptoms and suppressed the growth of the metastatic lesion for at least 4 months.

The current standard approach to the management of a life-threatening BM is surgery and radiotherapy. In the present case, we demonstrated that NSCLC with BM may be efficiently treated with the EGFR-TKI icotinib. A standard dose of icotinib reduced the size of the brain lesion and relieved the patient's symptoms as quickly as surgery. Icotinib decreased the size of the protrusion on the patient's forehead as well as the size of the brain mass in ~12 h, which was confirmed by recovery of left body function. This rapid effect may be attributed to two reasons: First, genetic analysis of the primary tumor identified an exon 19 mutation in the EGFR gene. It has been reported that primary tumor EGFR status is a good surrogate for EGFR mutation status of the BM, with a concordance rate of 93.3% (22). Second, our patient's brain had a large lesion, which disrupted the frontoparietal bone plate and diploe. This damage may have facilitated the transport of icotinib across the blood-brain barrier.

Therefore, our case suggests that EGFR-TKI treatment may be a quick, safe and effective option for patients with BM, particularly those harboring an EGFR mutation, with a poor functional status, or in an emergency situation.

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