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CASE REPORT

Brain metastasis in non-small cell lung cancer (NSCLC) patients with uncommon EGFR mutations: a report of seven cases and literature review

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ABSTRACT Brain metastasis (BM) arising from non-small cell lung cancer (NSCLC) with rare epidermal growth factor receptor (EGFR) mutations is quite rare. The prognosis and therapeutic effects of BM remain enigmatic. To the best of our knowledge, this is the first report to make a separate analysis of BM from NSCLC patients with original uncommon EGFR mutations. We retrospectively reviewed 7 cases of BM arising from 42 cases of uncommon EGFR mutated lung cancer in Tianjin Medical University Cancer Institute and Hospital. We also performed a literature review to assess therapeutic features and outcomes.

KEYWORDS Brain metastasis; NSCLC; uncommon EGFR mutations; EGFR-TKIs; brain radiotherapy; chemotherapy

Introduction

Brain metastasis (BM) is especially prevalent in patients with common epidermal growth factor receptor (EGFR) mutation positive non-small cell lung cancer (NSCLC)[1,2] and has been historically considered as a major determinant of overall survival (OS). It is one of the common causes leading to treatment failure. The survival time of these patients is approximately 7–12 months[3,4], according to recent reports. EGFR- tyrosine kinase inhibitors (TKIs) are frequently used as a standard treatment of BM from EGFR-mutation positive NSCLC[5,6]. Patients with uncommon EGFR mutations have lower response rates to EGFR-TKIs than those who have more common mutations. Platinum-based chemotherapy may be relatively effective for NSCLC with uncommon EGFR mutations[7]. However, reports of BM from NSCLC with uncommon EGFR mutations are extremely rare. Here, we reported 7 cases of BM arising from 42 cases of uncommon EGFR mutated lung cancer in our hospital. We also reviewed the literature to assess therapeutic features and outcomes.

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Cases report

Case 1

In April 2012, the patient (stage: T3N1M0 IIIa) had undergone wedge resection of an upper right lung neoplasm. The pathological result was mucous adenocarcinoma with micropapillary involvement. The genetic subtype was *EGFR* 20: 2369C > T (T790M). The patient received 18 cycles of adjuvant chemotherapy with pemetrexed plus carboplatin. Following the chemotherapy treatment, he received thoracic radiotherapy combined with pemetrexed for 2 cycles. Because of the EGFR-mutation status, we initiated treatment with gefitinib in January 2015. The treatment regimen was changed to afatinib in March 2015, due to the therapeutic effect. Unfortunately, he withdrew from afatinib treatment voluntarily 2 months later for financial reasons.

In September 2015, three and a half years later, brain magnetic resonance imaging (MRI) and positron emission tomography revealed metastasis in the patient's brain, left lung and mediastinal lymph nodes. He received bevacizumab combined with different regimens of chemotherapy for 14 cycles from September 2015 to November 2016. Currently, the patient has no neurologic symptoms, and has survived 5 years since diagnosis (**Figure 1**).

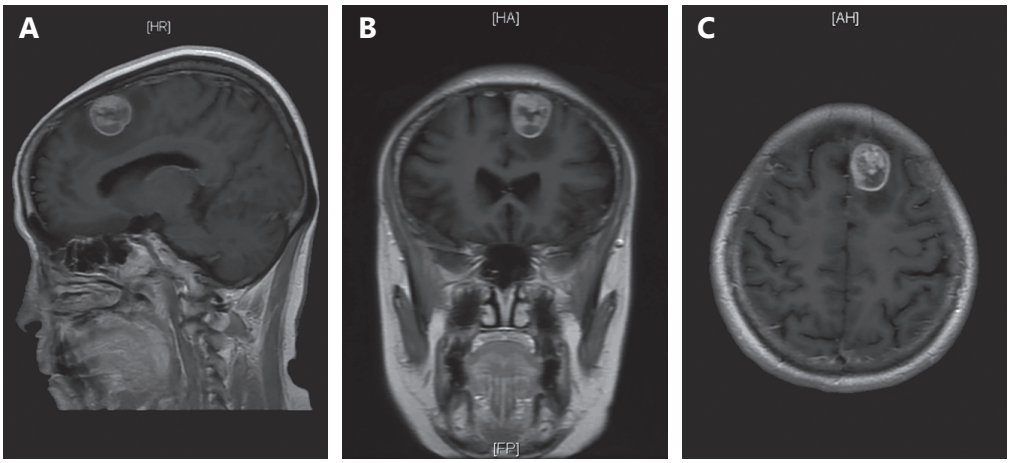

Figure 1 Case 1: brain magnetic resonance imaging (MRI) showed metastasis in the patient's brain in September 2015.

Case 2

A 69-year-old man with a history of smoking presented with bronchioloalveolar carcinoma of the right lung (stage: T2aN1M0 IIa). He had metastatic lymphadenopathy near the bronchi. A mutation in *EGFR* exon 18 (2156G > C; G719S) was detected.

In August 2011, he had undergone resection of the inferior lobe of the right lung and lymphadenectomy by video-assisted thoracic surgery. He was administered postoperative targeted therapy by erlotinib, and withdrew after 1 year. When he experienced numbness in the fingers of his right hand in November 2015, brain MRI revealed multiple fronto-parietal metastases. He received brain radiotherapy (42 Gy/10 f). After 6 months, in order to remove compression, he received cyber knife treatment (20 Gy/1 f) in his right brain ventricle (**Figure 2**).

At the last assessment, chest computed tomography scan and brain MRI suggested the patient was in stable condition. He has survived over 5 years since diagnosis (67+ months).

Case 3

T2aN0M0 (stage Ib) lung adenocarcinoma was diagnosed in a 56-year-old woman without a history of smoking. *EGFR* mutation analysis identified a mutation in exon 18 (2156G > C; G719S). BM was found 1 month after radical resection in March 2014. Four cycles of chemotherapy plus icotinib was administered, after which she received erlotinib for 3 months. Her subjective symptoms improved gradually within 7 months of the administration of TKIs. The patient is still alive 3 years after diagnosis.

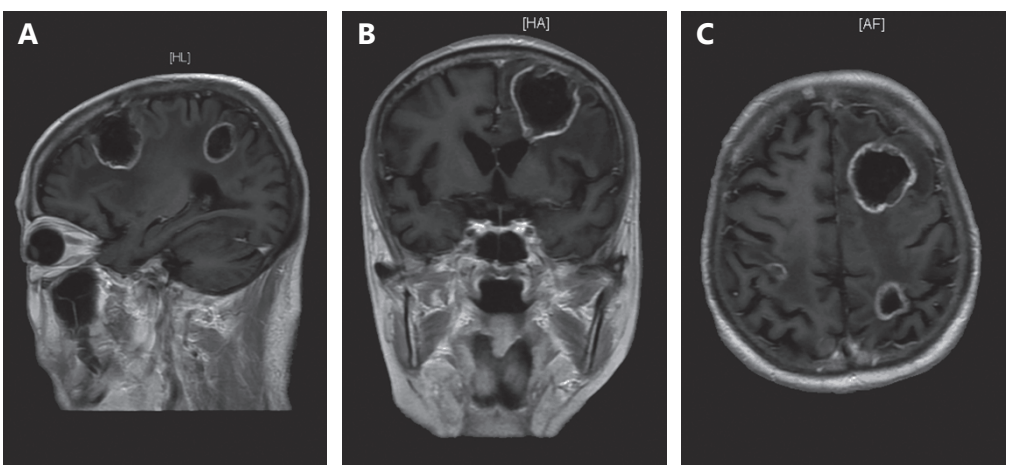

Figure 2 Case 2: pre-radiotherapy brain MRI revealed multiple fronto-parietal metastases in November 2015.

Case 4

A 53-year-old woman underwent resection of the inferior lobe of the right lung and lymphadenectomy when she was diagnosed with T2aN2M0 (stage- IIIa) lung adenocarcinoma with micropapillary involvement in March 2013. An *EGFR* mutation in exon 20 (2369C > T; T790M) was discovered. She received four cycles of adjuvant chemotherapy with pemetrexed plus carboplatin. In January 2015, metastasis was discovered in her occipital lobe. Erlotinib and gefitinib were administered until she died due to the primary tumor in October 2015 (**Figure 3**).

Case 5

A 70-year-old woman was diagnosed with lung adenocarcinoma (Stage: T1bN2M0 IIIa, micropapillary+). An *EGFR* mutation in exon 20: (2369C > T; T790M) was discovered. She underwent resection of the inferior lobe of the right lung and lymphadenectomy, followed by four cycles of pemetrexed plus carboplatin chemotherapy. Six months later, brain and bones metastases appeared. First-generation TKIs were administered for 1 year. She died in May 2015, 25 months after the diagnosis and 6 months after the withdrawal of TKIs.

Case 6

A 56-year-old man was diagnosed with lung adenocarcinoma (stage: T2aN2M0 IIIa, micropapillary+) with an *EGFR* mutation in exon 18 (2156G > C; G719S). He underwent excision plus lymphadenectomy. Adjuvant chemotherapy was started in April 2014. In the beginning of 2015, multiple metastases were found in his whole body, including the brain. The patient died on March 31, 2015, 1 year after the diagnosis.

Case 7

A 70-year-old woman with a history of smoking was diagnosed with undifferentiated lung carcinoma (stage: T2bN3M0 IIIb) in August 2013. A mutation in exon 18 (2156G > C; G719S) of *EGFR* was detected. Erlotinib was administered for half a year and chemotherapy with pemetrexed plus lobaplatin was administered through August 2014. Shortly after that, the patient developed bone metastasis and BM. She died due to cerebral hemorrhage in November 2014.

Summary

We observed 7 cases of BM from 42 lung cancer patients with uncommon *EGFR* mutations (2 men, 5 women). The median age was 62 years old (range, 53–70). Three cases were smokers and 4 were non-smokers. Four cases had mutations in exon 18 while the other 3 had mutation in exon 20. One case had stage I disease, 1 was stage II, and 5 were stage III. Six cases were administered first-generation EGFR-TKIs, and three cases received EGFR-TKIs after developing BM. Case 1 changed to afatinib and only case 2 received brain radiotherapy. The Chi-square test showed that lymph node metastasis and metastasis to other sites were significant factors for developing BM (P=0.018 and P=0.002, respectively). The major information of these cases is presented in **Tables 1–4**.

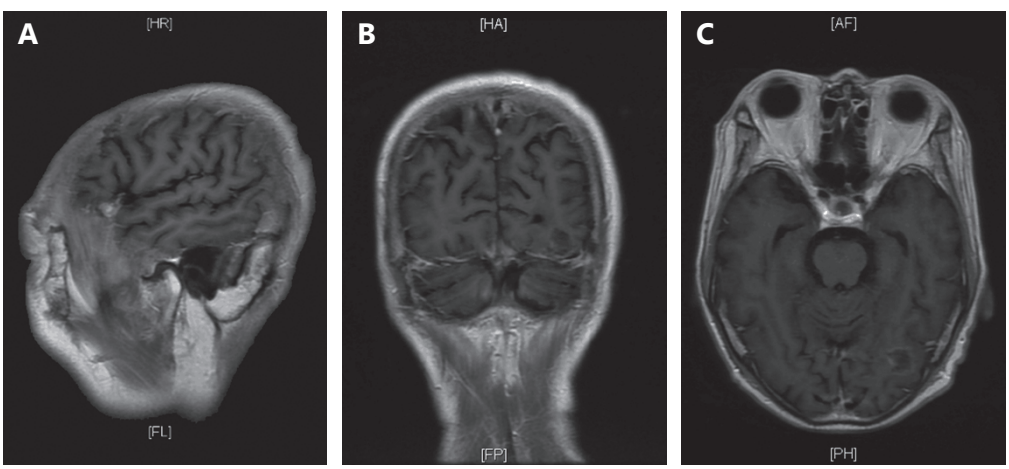

Figure 3 Case 4: metastasis was found in the occipital lobe in January 2015, 21 months after the first diagnosis.

Table 1 Essential information of the 7 cases

Case	Age/gender	Smoking status	Primary localization	TNM staging	Clinical staging	Micro papillary	Mutation localization
1	62/M	N	Upper lobe of right lung	T3N1M0	IIIb	Y	Exon 20 (T790M)
2	69/M	Y	Lower lobe of right lung	T2aN0M0	Ib	N	Exon 18 (G719S)
3	56/F	N	Lower lobe of right lung	T2aN1M0	IIa	N	Exon 18 (G719S)
4	53/F	N	Lower lobe of right lung	T2aN2M0	IIIa	Y	Exon 20 (T790M)
5	70/F	N	Lower lobe of left lung	T1bN2M0	IIIa	Y	Exon 20 (T790M)
6	56/F	N	Lower lobe of left lung	T2aN2M0	IIIa	Y	Exon 18 (G719S)
7	70/F	Y	Upper lobe of right lung	T2aN3M0	IIIb	N	Exon 18 (G719S)

M, male. F, female. Y, yes. N, no.

Table 2 Clinical features of the 7 cases

Case	Initial diagnosed date	BM diagnosed date	Death date	Symptom	Complication	Non-brain metastasis	Intracranial PFS
1	03/26/2012	08/27/2015	-	Headache	N	Left lung, pleura	41 months
2	08/17/2011	11/09/2015	-	Numb	N	N	49 months
3	03/20/2014	04/20/2014	-	N	N	N	1 month
4	04/03/2013	01/17/2015	10/14/2015	N	N	N	21 months
5	04/26/2013	10/23/2013	05/31/2015	N	N	Bone	5 months
6	03/12/2014	01/01/2015	03/31/2015	Numb	N	Bone	9 months
7	08/21/2013	07/04/2014	11/30/2014	N	Cerebral hemorrhage	Bilateral lung, bone	10 months

BM, brain metastasis. Intracranial PFS, intracranial progression-free survival. OS, overall survival. N, no.

Table 3 Summary of clinical information of treatment

Case	Surgery	Outcome	Brain RT	Response	Chemotherapy	Response	EGFR-TKIs	Response	Bevacizumab
1	Y	Successful	N	-	PC, DN, GN	SD	Gefinitib, Afatinib	Unevaluated	Y
2	Y	Successful	Y	PR	N	-	Erlotinib	SD	N
3	Y	Successful	N	-	Y	SD	Icotinib, Erlotinib	SD	N
4	Y	Successful	N	-	PC	PD	Erlotinib, Gefinitib	PD	N
5	Y	Successful	N	-	PC	PD	Y	SD	N
6	Y	Successful	N	-	Y	PD	N	-	N
7	N	-	N	-	PL	PD	Erlotinib	PD	N

Brain RT, brain radiotheraphy. Y, yes. N, no. PR, partial remission. SD, stable disease. PD, progressive disease. PC, pemetrexed+carboplatin. DN, docetaxel+nedaplatin. GN, gemcitabine+navelbine. PL, pemetrexed+lobaplatin.

Discussion

To our knowledge, this is the first report to make a separate analysis of BM from NSCLC with rare EGFR mutations. Approximately 20%–50% of NSCLC patients develop BM[1-3,8,9], which is associated with poor prognosis. The median survival time for patients with untreated BMs is only about 2 months, and it may increase to 3–6 months following whole-brain radiotherapy (WBRT)[3,4,8]. Recently, prognosis has been improved by using brain radiotherapy combined with chemotherapy, resulting in a median survival time ranging from 6 to 12 months[4,8,10]. There is a higher incidence

Table 4 Association of BM status with clinicopathological variables

Variable	*n*	BM status		*P*
		With BM	Without BM	
Gender				0.770
Male	14	2	12	
Female	28	5	23	
Age, years				0.782
< 60 (median)	20	3	17	
≥ 60	22	4	18	
Smoking				0.890
yes	19	3	16	
no	23	4	19	
KPS scale				0.269
≤ 80 (median)	22	5	17	
> 80	20	2	18	
Tumor location				0.570
Left lung	16	2	14	
Right lung	26	5	21	
Micro papillary				0.902
Yes	26	4	22	
No	12	2	10	
Clinical staging				0.068
I-II	25	2	23	
III-IV	17	5	12	
Primary T category				0.127
≤ 3 cm	23	2	21	
> 3 cm or multifocal lesions	19	5	14	
Lymph node metastasis				0.018
N0	23	1	22	
N1-N3	19	6	13	
Non-brain metastasis				0.002
Yes	15	6	9	
No	27	1	26	
Mutation localization				0.538
Exon 18	18	4	14	
Exon 20	20	3	17	
Exon 18+exon 20	4	0	4	

BM, brain metastasis, KPS, karnofsky performance status.

of BM in NSCLC patients with EGFR mutations (39.2%, compared to 28.2% for those without EGFR mutations, $P < 0.038$)[2]. Patients with mutation in exon 19 have the highest incidence of BM[11]. The current mainstream view is that EGFR-mutated NSCLC has a higher incidence of BM, but the survival time may be longer than wild -type EGFR NSCLC because of the use of EGFR-TKIs. Today, thanks to TKIs, NSCLC patients with EGFR mutations with BM at diagnosis achieve a median survival of approximately 18 months[10,12,13]. Therefore, the higher BM incidence in the EGFR-mutated group might partly be explained with a prolonged survival in the EGFR group. However, for uncommon mutations, the incidence of BM, the survival time and the treatment methods are still unclear. In a study of 4 NSCLC patients with uncommon EGFR mutations (one with a mutation in exon 18 and three with mutations in exon 20), only one had BM, giving a 25% incidence rate[11]. In our cases, the incidence rate of BM was 16.7% for patients with uncommon EGFR mutations, lower than expected. According to the Chi-square test, BM development was probably associated with lymph node metastasis and metastasis to other sites (P=0.018 and P=0.002, respectively; **Table 4**). Both are adverse prognostic factors. However, we cannot jump to a conclusion due to the limitation of our small sample size. The reason for this low incidence rate might be that many patients have died from the primary tumor and complications before they developed BM. The majority of NSCLC patients who developed BM survive for 3–6 months, and the 1-year survival rate is 10%[14]. A study showed that the median progression-free survival (PFS) and OS were better in patients with common EGFR mutations than in patients with uncommon mutations (15.5 *vs.* 3.9 months, $P < 0.001$; and 37.3 *vs.* 17.4 months, $P < 0.001$; respectively)[7]. The median intracranial PFS and OS of the 7 cases in this study were 9 months (1–49 months) and 30 months (12–67+ months). Moreover, the 1-year survival rate in our study was 100%, obviously superior to the expectation. It may predict a better prognosis and therapeutic effects of BM in these cases, especially for case 1 and case 2. Treatment of NSCLC with uncommon EGFR mutations is still controversial. Of these seven cases, six underwent targeted therapy. Case 6 did not undergo targeted therapy, which might explain why he had the shortest survival time (1 year, 18 months shorter than the median OS of 30 months). Three of seven cases underwent EGFR-TKI treatment after developing BM. The median usage time and survival time with BM of these three cases were 10 months (7–12 months) and 20 months (9–35+ months), respectively. The sensitivity to EGFR-TKIs of patients with EGFR mutations differ from those with wild-type EGFR. Patients with uncommon mutations usually have higher sensitivity than those with wild-type EGFR and lower sensitivity than those with common mutations[6,7,15-19], particularly with regards to first-

generation EGFR-TKIs (erlotinib, gefitinib, and icotinib) [16-18,20-22]. However, afatinib seems to be clinically active and well tolerated in many TKI-pretreated NSCLC patients harboring uncommon EGFR mutations[23-25]. Recent reports suggest that third-generation EGFR-TKIs (AZD9291 and AZD3759) may be an effective treatment for first- or second-generation EGFR-TKI-resistant NSCLC with EGFR mutations, depending on their effect as radiosensitizers and the high permeability of the blood brain barrier[26-28]. However, there are few studies exploring third generation TKIs and BM with rare mutations. In these seven cases, six were administered first-generation EGFR-TKIs as an important means of outpatient adjuvant therapy. Case 1 stopped using gefitinib and changed to afatinib due to the therapeutic effect. Since the administration time was short, we could not assess its contribution to his survival. His intracranial PFS and OS reached 41 months and 5 years, longer than the median intracranial PFS (9 months) and OS (30 months). As the only case receiving bevacizumab, case 1 also showed that bevacizumab therapy may be beneficial in combined treatment. Additionally, platinum-based chemotherapy may be relatively effective for NSCLC with uncommon EGFR mutations[7,22]. The addition of pemetrexed to gefitinib seems to provide clinical benefit for PFS compared with gefitinib monotherapy[29]. Six cases received systemic chemotherapy as the first-line therapy, while case 2 received brain radiotherapy instead. Brain radiotherapy combined with EGFR-TKIs seems to be the standard therapy and is well tolerated in patients with BM of EGFR-mutated NSCLC[5,8,12,30-36]. Intracranial PFS was improved in patients receiving upfront radiotherapy compared with those receiving upfront EGFR-TKI (37.9 *vs.* 10.6 months; $P < 0.001$)[37]. A recent multi-institutional analysis showed that using upfront EGFR-TKI and deferral of radiotherapy is related to shorter OS in EGFR mutated NSCLC patients with BM. The OS of patients who received stereotactic body radiation therapy followed by EGFR-TKIs was longer than patients who received WBRT followed by EGFR-TKIs[38]. However, for uncommon EGFR mutations, there is very little evidence to support the use of radiation therapy to treat BMs. Case 2 is the only stage I case and the only that received brain radiotherapy. The intracranial PFS and OS reached 49 months and 67 months, respectively, longer than the median 9 months and 30 months, respectively. Despite the interference of stage, this case with a desired response to brain radiotherapy might have important clinical implications. Neurological symptoms and comorbidities did not result in worse overall prognosis for patients with BM[39]. Even though cases 1 and 2 had symptoms like headache or numbness, they are still alive with ideal treatment effect.

In summary, in addition to lymph node metastasis and metastasis to other sites, patients with uncommon EGFR mutations are more likely to develop BM. Prognosis and the therapeutic effects on BM from NSCLC with uncommon EGFR mutations are probably better than expected. Brain radiotherapy might offer a clinical benefit in the treatment of BM arising from NSCLC patients harboring uncommon EGFR mutations. First-generation EGFR-TKIs and afatinib might also represent effective treatment options for patients with uncommon EGFR mutations with BM. The effect of the third-generation TKIs is worth more examination. Future studies are needed to evaluate the effect of bevacizumab therapy in this combined treatment. Unfortunately, the limited number of cases in our study weakens the solidity and impact of our findings and we were unable to address some of our objectives more clearly. Thus, more randomized controlled clinical trials with a larger number of cases are warranted.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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