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# Leptomeningeal Metastasis in Non-Small Cell Lung Cancer: A Report of Two Cases and Short Rewiev of Literature

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## Abstract

Central Nervous System (CNS) metastasis cause serious clinical deterioration in patient with Non-Small Cell Lung Cancer (NSCLC). Systemic cytotoxic agents, Whole Brain Irradiation (WBRT), oral targeted therapies and Intrathecal Chemotherapy (IC) are well known treatment options. In first case we aim to share two lung cancer patients at young ages with Leptomeningeal Metastasis (LM) treated with oral targeted therapies combined with WBRT.

**Keywords: Non-small cell lung cancer; Leptomeningeal metastasis; Neuroimaging; Epidermal growth factor receptor tyrosine kinase inhibitors; ALK inhibitor**

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## Introduction

CNS involvement of solid tumours in particular LM usually related to clinical deterioration and shortened survival. As survival of malignancies prolonged with developments in therapy area, incidence of LM is increases. Its frequency changes in 3% to 8% of all cancer types [1]. Best survival that can be reached with combined treatments ranges from 3 to 22 months [2]. Lung cancer, breast cancer and malign melanoma are primary tumours prone to metastasis to leptomeningeal tissue [3]. Frequency of LM in NSCLC is exactly 5% [4].

Its clinical presentation usually goes with neurological symptoms. These symptoms may vary from seizures, headache, dizziness, nausea and vomiting to encephalopathy [3]. The current diagnostic methods are cytological analyses of Cerebral Spinal Fluid (CSF) and Magnetic Resonance Imaging (MRI) of brain. Enhancement of dura, ventricular ependymal, ventriculomegaly and nodular enhancement in subarachnoid space are descriptive features of LM on MRI. If there is a clinical suspicion for LM, MRI should be preferred rather than lumber puncture [5].

Despite all treatment modalities LM is a still bad prognostic factor. Systemic chemotherapy, WBRT, IC, Ventricular-Peritoneal (VP) shunt operation and combining of them are treatment options but there isn't any optimal therapeutic approach [3]. Shunt operation is considerable for hydrocephalus and WBRT is an option against to oedema around focal metastatic lesions. LM isn't a suitable clinical condition for surgery. But depending on the location and number of metastasis surgery or Stereotactic Radio Surgery (SRS) might be an alternative choice. In patient with oligo metastatic CNS lesions surgery combined with WBRT provides better symptom control and survival [6].

IC is superior to systemic chemotherapy in terms of survival but standardization of IC is unclear due to using different drugs (methotrexate, cytosine-arabinoside, hydrocortisone, and thiotepa) in studies [7]. As the Blaney and Poplack [8] stated the agent to be used intrathecal route should be soluble, neurotoxicity free and suitable for intrathecal administration. Topotecan, mafosfamide, gemcitabine, busulfan and ACNU (3-[(4-amino-2-methyl-5-pyrimidinyl) methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride are agents under investigation for intrathecal use recently [5]. Ventriculo-lumbar perfusion is an alternative route to IC when increased intracranial

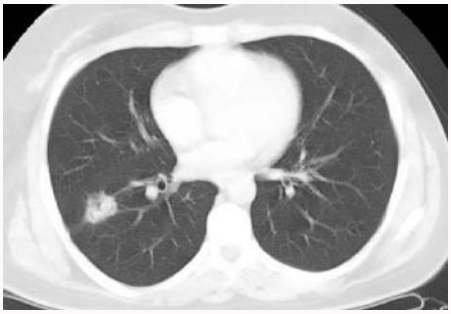

**Figure 1:** 26 mm × 25 mm mass on right lower lobe superior.

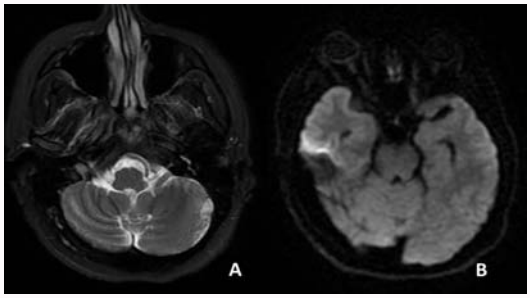


**Figure 2:** A) Significant enhancement on left cerebellar hemisphere; B) Thickening and enhancement of interhemispheric fissure and 6 mm × 7 mm nodular lesion on right parasagittal sulcus with oedema.

pressure is concerned. This method seems to provide better symptom control but it's not recommendable already due to side effects and lack of a standard application schema [5].

Nearly in last ten years many oral targeted therapies are approved by US Food and Drug Administration (FDA). In latest reports Progression Free Survival (PFS) and symptom control are seem to be achieved by oral targeted therapies in NSCLC [5]. Especially they are more successful in patients who have deletions in exon 19 and exon 21 L858R mutations. There are some reports suggesting erlotinib or gefitinib are more effective than other treatment modalities in terms of Overall Survival (OS) even they are used as re-challenge [9]. Erlotinib seems more effective than gefitinib when analysed amount of malignant cells in the cerebrospinal fluid [10]. In patients whose neurological symptoms are refractory to standard dose EGFR-TKI, high dose erlotinib is considerable [11].

Crizotinib is another TKI that is available for patient with ALK rearrangement. Frequency of ALK arrangement in NSCLC is exactly 5% and 4% of them have LM [12]. OS for advanced NSCLC patients harbouring ALK mutation is 26.9% according to phase 1 and phase 2 studies. These patients are mostly under age of 65, non-smoker or minimal smoking history and adenocarcinoma histopathology [13]. Even crizotinib's penetration to CSF is low there some reports demonstrating its efficacy on CNS metastasis. But current literature includes a dilemma that CNS is like a dominant site of disease progression under crizotinib treatment. In this instance Alectinib and ceritinib are alternative ALK-targeted TKIs for patients with crizotinib resistance. But mechanisms of acquired resistance to ALK inhibitors are still unclear and alternative agents that are more potent against to CMS metastasis are under investigation [14]. So we want to discuss LM metastasis in NSCLC along with two patients having oncogene driven.

## Case Presentation-1

A 34-year-old non-smoker woman admitted to our department with chest pain and cough. A 26 mm × 25 mm speculated lesion with Standardized Uptake Values (SUVs) 5.8 was detected on right lower lobe superior with Positron Emission Tomography (PET-BT) (Figure 1). There were not lymph node involvements. Her cranial MRI revealed no metastasis. She was diagnosed pulmonary adenocarcinoma and her pathological stage was T2AN0M0 after right Video-Associated Thoracoscopy (VATS) + right lower lobectomy + lymph node dissection on June 2013. She was treated with four cycle adjuvant chemotherapy with vinorelbine-cisplatin regimen. While she was on following period after last chemotherapy (September 2013) on October 2015 she was admitted to emergency department with nausea, vomiting, ptosis of the right eye, blurred vision and epileptic attack. After controlling her neurological symptoms, a Diffusion-Weighted cranial Magnetic Resonance Imaging (DW-MRI) was performed. MRI findings were a 6 mm × 7 mm diameter in nodular lesion characterized significant enhancement on left cerebellar hemisphere, thickening and enhancement of interhemispheric fissure and 6 mm × 7 mm nodular lesion on right para sagittal sulcus with oedema around (Figure 2A and 2B). These were suggestive findings for LM. Her neurological symptoms were controlled with anti-epileptic and anti-oedema treatment following with 30 Gy WBRT with ten fractions. There weren't any findings suspicious for recurrence of malignancy on PET-BT that performed again. Her pathology specimen re-investigated for EGFR mutations and while receptor tyrosine kinase (ROS1) and anaplastic lymphoma kinase (ALK) was negative; exon 19 deletion was detected. Her therapy was continued with erlotinib and she is still under treatment and following period with EGFR-TKIs.

## Case Presentation-2

A 29-year-old male with 15 pack-year history of smoking admitted to our department with dyspnoea and dry cough. PET-BT was performed upon detection of right hilar enlargement on chest X-ray. There were a FDG avid-mass on right hilum with multiple mediastinal and right supraclavicular lymphadenopathy. PET-BT showed multiple lytic metastases to ribs, sacrum, left femur neck, thoracolumbar vertebra and right acetabulum (Figure 3A and 3B). Cranial CT revealed no intracranial metastasis. Fibre Optic Bronchoscopy (FOB) was negative for endobronchial lesion so supraclavicular lymph node aspiration biopsy was performed. His pathological diagnosis was adenocarcinoma with TTF1 and napsin positive (June 03, 2014). Radiotherapy (2,000 cGy) with four fractions was performed to spine metastasis then June 12, 2014 first cycle of pemetrexed and cisplatin were administrated. Seven days after the first chemotherapy he was presented with confusion, right hemiparesis. Cranial DW-MRI revealed focal hyper intensity on right subcortical white matter on flair sequences and hyper intensity on bilateral hemispheres, more prominent on the left, on T2 weighted images suggesting LM (Figure 4A and 4B). Patient received WBRT for ten days together with anti-oedema treatment. Neurological symptoms were regressed but due to poor clinical condition he couldn't be continued with systemic chemotherapy. After detection ALK re-arrangement, ALK-targeted TKI (crizotinib) was started (July 02, 2014). Even he didn't use his medicine regularly almost complete regression was obtained according to PET-BT performed on August 2014 (Figure 3C and 3D). Although any side effects of drug weren't seen, patient interrupted the treatment. He died because

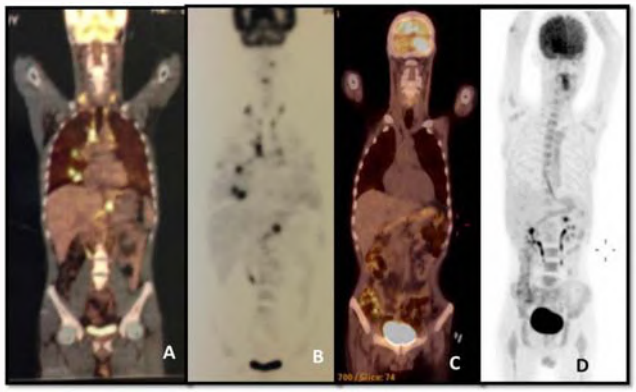


**Figure 3:** A & B) FDG avid-mass on right hilum with multiple mediastinal lymphadenopathy, multiple lytic metastases to ribs, sacrum, left femur neck, thoracolumbar vertebra and right acetabulum; C & D) Complete regression after crizotinib.

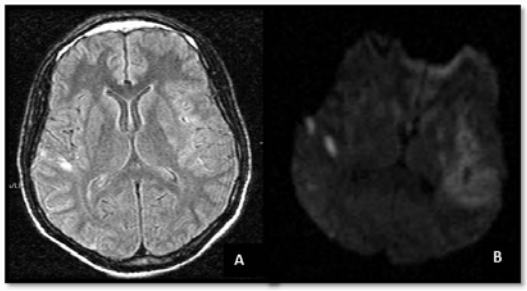


**Figure 4:** A) Focal hyper intensity on right subcortical white matter on flair sequences of DW-MRI; B) Hyperintensity on bilateral hemispheres, more prominent on the left, on T2 weighted images of DW-MRI.

of pneumonia and respiratory failure seventy-eight days after the crizotinib.

## Discussion

Leptomeningeal metastasis is a difficult clinical condition to handle that impairing quality of life and shortened survival in patients with lung cancer. The median survival in patients with LM is exactly 4-6 weeks without any treatment [15]. Non-small cell lung cancer especially adenocarcinoma subtype is one of common solid organ cancer accompanied by LM with frequency of 5% [4]. Similarly present cases were diagnosed with lung adenocarcinoma with different initial stages. Different reports about the median time from first diagnosis of lung cancer to LM are available in literature. It is mostly between 1-2 years and has prognostic significance [3,5]. But according to a retrospective study with 108 NSCLC patients, LM was obtained before 12 months and it also varies according to the treatment protocols. It is expected to be lower in patients receiving oral targeted therapies [14].

Although common clinical findings are seizures, headache, dizziness, nausea and vomiting, patients' clinical presentation may be more severe like encephalopathy [3]. Our first case admitted to emergency department with epileptic attack and the other patient had confusion, right hemiparesis. In case of clinical suspicious, cytological analyse of CSF is gold standard but cranial MRI is less invasive so it's preferable in clinical practices. Diffuse or nodular enhancement of the leptomeningeal is most common radiological appearance. Both patients were performed DW-MRI.

WBRT is not first choice in diffuse involvement of leptomeninges, except coexistence of brain metastasis and nodular or symptomatic linear LM [7]. Both of present cases were performed WBRT first for cranial metastasis (Table 1). It was remarkable in first case that, during WBRT neurological symptoms like epileptic attacks, nausea and vomiting were decreased but blurred vision and ptosis of the right eye didn't respond radiotherapy well. She couldn't be able to walk without support. Dramatically, after initiating erlotinib, better and faster clinically respond was obtained than WBRT. Even TKIs penetration to CNF is limited they are advantageous in terms of OS and PFS especially in patients with EGFR mutation who is non-smoker and female gender [4].

Crizotinib, a multi-targeted TKI against to MET, ALK and ROS1 is known to be effective both primary and metastatic brain tumours despite its' low concentration in CSF. To our knowledge there are some reports demonstrating that brain is a common site of recurrence in ALK naïve NSCLC. But when starting crizotinib after diagnosis the brain metastasis, CNS or systemic progression is unexpected for majority of patients within the first year [16]. Similarly in present case with ALK rearrangement recurrence after first treatment protocol was obtained in the form of brain metastasis and showed good response to WBRT. Control PET-BT revealed regression of primary, extracranial and cranial metastatic lesions after one month from crizotinib. But we couldn't determine impact of crizotinib on PFS or OS due to patients' bad compliance to treatment.

In patients having ALK-rearrangements or EGFR-mutated there isn't any data demonstrating the best treatment approach to LM. But

**Table 1:** Descriptive characteristics of patients.

| Variable | Patient 1 | Patient 2 |
|---|---|---|
| **Age and Gender** | 34 –Female | 29- Male |
| **Histology** | Adenocarcinoma | Adenocarcinoma |
| **Smoking Status** | Never Smoked | 15 packet-year |
| **Initial Stage of Disease** | Stage IB | Stage IV |
| **Modality of LM Diagnosis** | Diffusion-weighted cranial magnetic resonance imaging | Diffusion-weighted cranial magnetic resonance imaging |
| **Concurrent Brain Metastasis** | Not present | Not present |
| **Brain metastases before LM diagnosis** | Not present | Not present |
| **Targeted therapy before LM** | No | No |
| **Presenting Symptom** | Epileptic attack and ptosis of the right eye | Confusion and right hemiparesis |
| **Time to diagnosis of LM** | 28 months | 16 days |
| **Survival** | Under follow-up | Died (survival time is 58 days) |

to best our knowledge, performing targeted therapies after WBRT is related to prolonged survival. WBRT following with systemic chemotherapy is also suggestible approach [3-15]. In this study it is a limitation that it is not possible to compare targeted therapies to systemic chemotherapy due to continuing treatment with erlotinib/crizotinib after WBRT.

In present EGFR-mutated case erlotinib was preferred as TKI rather than gefitinib. Even both drugs' have low penetration to CSF, erlotinib superior to gefitinib in terms of cytological conversion rates [10]. Also according to a comparative study among patients with pre-existing brain metastases, time to neurological progression is longer in erlotinib than gefitinib [17]. Osimertinib, a third generation inhibitor, has better penetration efficacy to CSF than first generation TKIs so when resistance was occurred to first-line targeted therapy osimertinib should be considered [7].

Though LM is a poor prognostic factor in itself, performance status is another predictor of survival among patients with LM. Contribution of different treatment modalities to survival is controversial. There are some reports, suggesting combined treatments with WBRT, IT chemotherapy or TKIs can improve OS up to 12 months [3,18]. But it might be due to exclusion of patients with poor performance status. Present cases are young, didn't have any comorbidities and both of them treated with WBRT following with TKI therapies after diagnosis of LM. Although the first patient is still under follow-up, patient with ALK-rearrangement died after fifty-eight days after diagnosis. These survival differences might be due to patients' different initial stage and ECOG [3]. Because she was diagnosed at the stage of IB and in good performance status but second case had multiple metastasis and bad medical condition (Table 1). Eventually, we think ECOG and disease stage can influence survival in NSCLC patients with leptomeningeal involvement.

EGFR-TKI therapy is related to extended survival in patients with curtain or probable EGFR-mutated [2,3]. Time between first diagnosis and LM was exactly 28 months and CNS was the first recurrence side similar to existed data [2]. Progression free survival is about 7 months in EGFR-mutated NSCLC patient with brain metastasis [2]. In present case any sign of progression wasn't determined during 4 months of treatment with erlotinib.

Even its' penetration to CSF is low, crizotinib is a successful agent to control systemic and intracranial disease in ALK re-arranged NSCLC patients. To the best our knowledge time to intracranial recurrence is changes between 2 weeks to 79 weeks [16,19]. In our patient his LM was obtained after two weeks (Table 1). Good performance status, absence of extracranial metastasis and no prior treatment with ALK-targeted TKI are related to good prognosis and nearly over 1 year PFS is expected for these patients [16,19]. Present case didn't have prior treatment with crizotinib but his performance status was bad and he was at the stage of 4 at the time of diagnosis. Even his neurological symptoms responded well to crizotinib he died 58 days after the treatment (Table 1).

Even it wouldn't be right to make a generalisation juts by case reports, in NSCLC patients with LM, combined therapy with WBRT and targeted therapies are associated to prolonged survival. Neurological symptoms decreased faster with targeted therapies than systemic chemotherapies. But performance status, stage of disease and presence of extracranial metastasis are other independent prognostic factors. Nevertheless acquired resistance to TKIs still remains as an obstacle. So especially in patients with prior history of TKI, a large populated study is needed to determine the best initial targeted therapy.

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