Spatial Tumor Heterogeneity in a Young Female with Lung Adenocarcinoma and Brain Metastasis

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ABSTRACT

Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are the two different forms of lung cancer, the latter subtype accounts for approximately 85% of cases. Lung cancer is estimated to be the main cause of all cancer deaths, accounting for nearly 1,800,000 deaths globally in 2020.

In this clinical case, we describe a female patient with non-specific symptoms over an approximate duration of one and a half years. Metastatic lung adenocarcinoma was diagnosed after the onset of severe neurological symptoms, brain surgery, and historical analysis of the large pathological brain mass. Following this, the tumor in the lung, which was small in size and the sole metabolically active site of the disease, was surgically removed. The recurrence in the brain and the onset of new neurological symptoms occurred rapidly—within three months, necessitating a second operation. Histological examination of the primary tumor and metastasis unveiled significant disparities—the primary tumor was moderately differentiated with PD-L1 expression (programmed death-ligand 1) within the range of 1 to 49%, while metastasis was poorly differentiated and PD-L1 negative, both absent of EGFR mutations (epidermal growth factor receptor) and ALK fusion (anaplastic lymphoma kinase). Following two brain operations, the patient underwent three-dimensional conformal radiation therapy (3D-CRT). Subsequently, the initiation of systemic therapy was postponed by a two-month interval due to the activation of chronic hepatitis C virus infection.

This case study contributes to the growing body of knowledge aimed at enhancing our grasp of tumor heterogeneity and dynamics of progression.

Keywords: Lung cancer, non-small cell lung cancer, tumor heterogeneity.

1. Introduction

The most prevalent subtype of NSCLC is adenocarcinoma [1]–[3]. Systemic symptoms associated with lung adenocarcinoma encompass cachexia, muscular atrophy, vomiting, fatigue, and significant weight loss. Furthermore, patients may manifest localized tumor invasion-related symptoms such as dyspnea, hemoptysis, wheezing, cough, dysphagia, and conditions like pleural or pericardial effusion and paralysis of the phrenic nerve [4]. Symptomatic disease significantly undermines the overall health and quality of life of patients. Approximately 57% of NSCLC patients present with metastatic disease, and 20% specifically exhibit brain metastases (BM) upon initial diagnosis. In addition, an estimated 25% to 50% of individuals will develop BM throughout the illness [5]. Clinical manifestations of BM encompass symptoms such as headaches, seizures, and localized neurological and cognitive impairment [6].

Clinical data indicates that individuals diagnosed with NSCLC are more likely to develop BM when the primary tumor is larger. The occurrence of BM is significantly higher when the initial tumor measures 3–7 cm or larger [7].

The presence of BM exerts an influence not only on neurological symptoms and quality of life but also on overall survival. Empirical observations indicate a one-year survival rate of approximately 59% for individuals with BM, diminishing to around 43% at the two-year mark. Furthermore, the progression-free survival rates stand at...
respectively [8].

Two primary treatment modalities for BM include surgical intervention and radiation therapy. For individuals with well-controlled systemic diseases, surgical tumor removal has demonstrated efficacy in mitigating edema, alleviating compression, addressing mass effects from metastases, and serving diagnostic biopsy purposes. Tailored to factors such as size, location, and quantity of BM, radiotherapy can be administered through various modalities, including whole brain radiation therapy, 3D-CRT (facilitating precise radiation dose calculation, computer-optimized treatment planning, and computer-controlled treatment delivery), and stereotactic radiosurgery (SRS). Clinical data indicates that patients with BM tend to have a longer life expectancy when opting for operative therapy instead of radiation treatment. The median survival for those undergoing surgery is 40 weeks, whereas for those receiving radiation treatment, it is 15 weeks. Moreover, in comparison to radiotherapy alone (52%), surgery reduces the likelihood of local recurrence by 20% [9]. Approximately 40% of cases exhibit progression of BM after resection. Additionally, around 10%–34% of patients encounter a recurrence within a year following appropriate treatment for metastasis [10].

The incidence of BM is higher in NSCLC patients harbouring oncogenic driver alterations, specifically EGFR and ALK. Clinical data is available on the effectiveness of targeted therapy using tyrosine kinase inhibitors. In cases lacking actionable driver mutations, the management of new or progressive BM poses a challenge and remains uncertain. This subgroup constitutes approximately 60% of all NSCLC cases [11]. Only a small number of studies have examined the relationship between tumour biology in BM and primary tumor. It has been suggested that distinct expressions may emerge as a result of the unique immunological environment. According to evidence from clinical trials, up to 86% of patients have concordant PD-L1 expression in both the primary tumor and BM [12]. Discordance in PD-L1 expression is relatively uncommon, typically reported in cases where the primary tumor demonstrates expression levels between 1 to 50% [13]. The rationale for the administration of immunotherapy is theorized based on the presumption that the blood–brain barrier is typically impermeable to anticancer agents characterized by large molecular weight and low solubility [11]. This impermeability is attributed to the presence of epithelial-like tight junctions within the capillary endothelium [11], [14]. Immune checkpoint inhibitors play a crucial role in enhancing the host’s innate immune response against tumor cells. Notably, BM often exhibits dense infiltrations of tumour-infiltrating lymphocytes. Given that immune checkpoint inhibitors function by alleviating the inhibition of T cells by tumor cells, the trafficking of peripherally activated T cells into the central nervous system is deemed perhaps more crucial than the direct penetration of the blood–brain barrier by the antibodies themselves [11].

Observational study reveals that around 92% of cases exhibit concordant EGFR expression, 87% show concordance in KRAS (Kristen rat sarcoma virus) mutation and a high and consistent level of concordance is observed in ALK mutations between the primary tumor and metastases [13].

Nowadays, treatment of systemic NSCLC disease is tailored, including chemotherapy agents, immunotherapy and target therapy [16], [17]. Patients with BM who are active, untreated, or symptomatic have generally been excluded from most immune-oncology trials. That being said, Hendriks et al. collected prospective data from 1,025 patients with NSCLC who were treated with immune checkpoint inhibitors at five different European hospitals, reporting similar response rates overall in patients with and without BM [18].

The objective of presenting this case is to delineate a complex diagnostic trajectory, swift progression of BM following the initial operation, and the spatial histological heterogeneity that presents a challenge in determining suitable systemic treatment.

2. Case Report

The patient, a 48-year-old female, visited her general practitioner (GP) in the middle of 2021 after she experienced chest pressure and upper back pain. The preliminary physical assessment, electrocardiogram, and chest radiography yielded no discernible pathological findings. The patient worked as a cleaner. One of her detrimental habits was smoking, she had been a daily smoker since the age of 16 (approximately 32 years in total), consuming one pack of cigarettes per day, which she had now reduced to 15 cigarettes daily. She had one daughter. The patient denied alcohol consumption and there is no family history of cancer. The patient’s medical history did not include any chronic diseases. She had only undergone one surgical procedure—myomectomy in 2018.

GP referred the patient to both a cardiologist and a neurologist, yet neither specialist detected any underlying pathology. For approximately one year, the patient’s symptoms were managed through the administration of a range of non-steroidal anti-inflammatory drugs and gabapentin (anticonvulsant medication primarily used to treat partial seizures and neuropathic pain).

The patient first noticed a restriction in her left arm’s range of motion in November 2022, specifically in terms of both elevation and flexion. She began experiencing persistent cephalalgia and muscular weakness a month later. As the symptoms progressed, her complaints included an unsteady gait, tremulous legs, and an increased frequency of right-sided headaches. Concurrently, she exhibited severe symptoms of depression and substantial weight loss - 20 kg in four months. Subsequently, in April 2023 she visited her GP once more. Due to her neurological symptoms, the patient was transferred to the secondary medical facility, where a computed tomography (CT) scan of the head was performed, revealing findings suggestive of a potentially malignant tumor measuring approximately 4.6 × 3.2 cm located in the left frontal lobe (see Fig. 1).

After receiving the results of the CT findings, she was transferred to the tertiary medical facility, where she received symptomatic treatment, and a magnetic resonance imaging (MRI) of the head was conducted (see Fig. 2).
A polymorphic, polycyclical tumor that spreads into the brain is in the left frontal lobe and is connected to the meninges as well as the basal, medial, and lateral regions of the frontal lobe. Tumor maximum sizes C-C and A-P exceed 5 cm, while tumor maximum size L-L was less than 5 cm. Deformation and peripheral oedema are visible in the middle structures.

On April 28, osteoplastic trepanation with tumor evacuation was performed. Histological findings in macroscopically 5 × 6 × 1.5 cm tissue size specimen revealed high differentiation grade (Grade 3) adenocarcinoma, immunohistochemistry: CK AE1/3 positive, CK7 positive, CK20 negative, p40 positivity was observed in individual cells, ER-negative, GATA3 negative, PAX-8 negative, mammaglobin negative, TTF1 positive in the malignant cell nucleus, napsin-A staining was intensely positive. The presence of positive immunostaining for TTF1 and napsin-A suggests metastatic lung adenocarcinoma.

Following the results of the pathological report, both a chest and abdominal CT scan (Fig. 3A) and a positron emission tomography scan (PET-CT) were performed (Fig. 3B).

Following the examinations, a bronchoscopy was performed to confirm the presence of the primary tumor. However, since it did not reveal malignant cells, the multidisciplinary tumor board recommended resection of the tumor for further evaluation. On June 21st, she underwent a video thoracoscopic resection of the left lung IV segment and subaortic lymphadenectomy. Histological findings revealed an intermediate-grade (Grade 2) pT1b lung adenocarcinoma, with no evidence of metastasis in the resected subaortic lymph nodes. Resection margins were clear (R0), tumor was found to be negative for EGFR and ALK mutations. However, it showed positive PD-L1 expression with a tumor proportion score (TPS) ranging from 1% to 49%. The final diagnosis was: stage IV lung adenocarcinoma T1bN0M1 with brain metastasis.

The multidisciplinary tumor board recommended systemic therapy. When the patient arrived for her initial round of systemic therapy (92 days after brain mass surgery), she had developed tingling sensations in the little finger of her right hand, and her headaches had occurred. A CT scan of the head was performed, revealing a malignant mass in the left frontal lobe (Fig. 4).

In the right frontal lobe, there is once more evidence of a polycystic, round-shaped, well-demarcated, non-homogeneous, vascular, aberrant formation measuring approximately 2.9 × 4.1 × 3.1 cm and accompanied by peripheral effusion. About 1.3 × 1.6 × 1.0 cm in size, a second round-shaped contrasting structure linked to falx cerebri is visible in the anterior basal region of the frontal lobe. It is located farther to the left. Although falx cerebri has been somewhat shifted to the right, the intermediate structures have not yet undergone any additional notable displacement.

After reviewing the tumor size, location, and clinical symptoms, decision in a multidisciplinary tumor board was made to operate - osteoplastic trepanation with tumor excision (surgery date-August 4). Macroscopically tissue size was 6 × 4.5 × 1 cm. Histological findings revealed high differentiation grade (Grade 3) adenocarcinoma, immunohistochemistry: CK 1/3 positive, CK 7 positive, CK 20 negative, TTF1 nuclear expression positive—metastatic involvement by lung adenocarcinoma. Immunohistochemistry revealed ALK, EGFR and PD-L1 (0%) negative tissues.

After the second brain surgery, the multidisciplinary tumor board recommended whole-brain irradiation. The patient underwent 3D conformal radiation therapy with a single dose per fraction of 3 Gy and a total dose of 30 Gy from August 24, until September 6. When the patient arrived for her initial round of systemic therapy, her blood test showed elevated liver enzymes: ALAT 395 U/L, ASAT 237 U/L. Consequently, the initiation of systemic therapy was postponed and the patient was referred to a hepatologist for specific treatment.

Following the normalization of liver enzyme tests, the patient commenced systemic therapy with paclitaxel and carboplatin. Concurrently, documentation for the reimbursement of atezolizumab and bevacizumab was prepared. During the last visit, the patient did not exhibit any new neurological symptoms and did not require assistance in her day-to-day activities, indicating both cognitive and physical independence.

3. DISCUSSION

In our clinical case, we described a young female patient. Statistical data reveals that only approximately 10% of NSCLC cases are diagnosed in individuals below the age of 55 [19]. Consistent with prior research findings, participants in younger age cohorts tended to be female, non-smokers, and advanced adenocarcinoma. Our patient conformed to this profile, except for the divergence in smoking status [20].

Fig. 1. CT scan on 19.04.2023 showed malignant formation in the left frontal lobe measuring approximately 4.6 × 3.2 cm (in the axial plane). Vascular oedema and compression of the left lateral frontal horn and the third ventricle are evident, with no significant dilation in the ventricular system. There is a midline shift towards the right, measuring approximately 8 mm.
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Fig. 2. MRI performed on 25.04.2023 showed tumor in the left frontal lobe and surrounding vascular oedema AxT1 3D (A), Ax T2 FLAIR 3D (B) and Sag FLAIR T2 3 mm rec (C).

Fig. 3. (A) CT scan on 11.05.2023 showed a lesion measuring $1.1 \times 0.9$ cm in the lingula of the left lung, which extends to the S4 bronchus; (B) PET/CT on 08.06.2023 showed in the upper lobe of the left lung, Sg3, a peripheral hypermetabolic lesion is present, likely indicative of tumor (PET/CT positive), additionally, a slightly asymmetric hypermetabolic small lymph node at the hilum of the left lung raises suspicion of metastasis (PET/CT weakly positive).

Fig. 4. CT on 28.07.2023 with iodine-based contrast showed a recurrence of the BM.

The range of potential differential diagnoses for brain lesions is extensive. While BM typically is multiple, the occurrence of solitary brain metastasis is not uncommon, with incidence ranging from 25% to 45% [21]. According to a clinical study by Tse [22], over 60% of patients with BM experience clinical symptoms. Nodular solid enhancement can be observed in various pathologies: metastatic disease, lymphoma, sarcoidosis, vasculitis, demyelinating disorders, as well as infections such as tuberculosis, toxoplasmosis, and fungal diseases. In the case of ring-enhancing lesions, the most prevalent aetiologies include high-grade glioma, metastases, abscesses, and demyelinating diseases [21], [23]. Hence, the initial decision to pursue surgery was influenced by the neurological symptoms, and to differentiate among the various aforementioned potential differential diagnoses. Upon detecting tumor recurrence, the treatment decision was further informed by the goal of mitigating neurological symptoms and considering overall survival, particularly given the reported superiority of surgical intervention in this context [9], [24]. Decision also aligns with Recursive Partitioning Analysis classification recommendations, where surgical therapies are deemed most suitable for patients under the age of 65 with brain metastases, particularly when the primary tumor is NSCLC and does not exhibit extracranial metastases. Our patient meets these requirements [25].

Significantly, it has been reported that resection effectively alleviates symptoms, enhances functionality, and reduces discomfort [24]. In our case, these outcomes were achieved, contributing to the attainment of a favorable health-related quality of life. It has been documented that neurocognitive capacity declines in approximately 90%, [26] of cases with similar conditions. Remarkably, in this
instance, despite undergoing two brain surgeries and having a substantial mass of metastases, the patient exhibited the retention of both cognitive and functional abilities throughout the observation period.

Literature elucidates heterogeneity across diverse components within the cells themselves and the cellular microenvironment. It distinguishes between spatial heterogeneity, which involves differences in characteristics such as genetic information and cell morphology within the primary tumor or between the primary tumor and the metastases, and temporal heterogeneity, primarily manifested by the polyclonal properties of tumors that evolve over time [27]. According to the results of a clinical study conducted by Camy et al., PD-L1 expression exhibited concordance between the main tumor and brain metastases in 75% of cases (n = 223 patients) [12]. In a smaller study by Batur et al., concordance was observed in 62.5% of patients (n = 24) [28]. Another study by Tonse et al. (n = 230) reported concordance in approximately 81% of tumors [13]. Demonstrating a range of variability, the concordance rates reported in these studies range from as high as 81% [13] to 62.5% [28]. The choice of immunotherapy for the patient’s treatment is presently a subject of debate. Particularly in this case, the primary tumor displays spatial heterogeneity, notably concerning differentiation and PD-L1 status. The National Comprehensive Cancer Network guidelines recommend first-line immunotherapy for patients with PD-L1 status ranging from ≥1% to 49% in conjunction with chemotherapy [29, 30]. However, although the primary tumor fell within this range, the metastasis did not. The combination increases overall survival and progression-free survival. However, the majority of NSCLC immunotherapy studies have excluded individuals with untreated or unstable brain metastases. Consequently, the overall data on immunotherapy in these patients is currently somewhat limited. Nevertheless, due to their favorable prospects for survival, individuals with brain metastases often receive immunotherapy in routine clinical practice [31].

A comprehensive meta-analysis exploring prevalent gene alterations in NSCLC reveals that brain metastases tend to arise in tumors with EGFR mutations (29.4%), ALK mutations (34.9%), KRAS (30.2%), ROS1 (32.2%), and RET (28.8%) changes. Next-generation sequencing (NGS)—has made molecular profiling more precise, but adds complexity to the treatment decision-making process.

Despite a delayed diagnosis and the significant extent of brain metastases, the local implementation of treatment strategies, coupled with early detection of brain metastasis recurrence, can markedly improve patients’ functional and cognitive capabilities, as well as their overall quality of life. The presence of spatial tumor heterogeneity, coupled with limited clinical trial data in patients with brain metastases, adds complexity to the treatment decision-making process.

5. Declarations

All procedures performed were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments. The authors declare that they have no competing interests.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

REFERENCES

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