Case report

Isolated progression of miliary brain metastasis in a patient with stable lung adenocarcinoma successfully treated with whole-brain radiotherapy: A case report

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ABSTRACT

Miliary brain metastasis is a rare form of metastasis commonly associated with advanced stages of cancer. In this article, we report a case of a 38-year-old male with solitary progression of miliary brain metastasis originating from stage 4 EML-ALK-positive lung adenocarcinoma. Multiple brain lesions were first detected upon the patient’s inclusion in a brigatinib clinical trial. The brain lesions dissipated, and the lung and bone lesions decreased in size after starting the brigatinib therapy; however, the brain lesions later increased in number. A biopsy revealed miliary brain metastasis of lung adenocarcinoma. The patient was successfully treated with whole-brain radiotherapy, in addition to brigatinib. This case suggests that it is possible for an isolated miliary brain metastasis to occur during the effective suppression of systemic cancer progression. Whole brain radiotherapy while continuing effective systemic therapy is a good strategy for such patients.

1. Introduction

Miliary brain metastasis is primarily seen in patients with adenocarcinoma of the lung and breast. It is characterized by the bilateral presence of myriad metastatic foci throughout the cerebellar tent [1]. It is rare, with a reported incidence of 2.4% (4 out of 163 cases) for brain-metastatic lung cancer and 3.8% (21 out of 546 cases) for brain-metastatic breast cancer [2,3]. Since miliary brain metastasis is most frequently identified in the advanced stages of cancer [4–6], it has an extremely poor prognosis (median survival-6.5 months), and there is little data regarding its treatment [2].

Herein, we report the case of a patient with miliary brain metastasis of lung adenocarcinoma in whom isolated progression of the brain metastasis was observed despite effective control of the primary lung lesions and bone metastatic lesions with brigatinib, which is an anaplastic lymphoma kinase (ALK) inhibitor. The brain lesions were successfully treated with whole-brain radiotherapy, and the patient survived for an extended period after the miliary brain metastasis was detected.

2. Case report

A 38-year-old man who had been diagnosed with stage 4 EML-ALK-positive lung adenocarcinoma four years previously was referred to our neurology department for diagnostic evaluation of unusual brain MRI finding. Vertebral metastasis was detected at the time of lung cancer diagnosis. Brain magnetic resonance imaging (MRI) did not show any abnormalities (Fig. 1 A, B). The patient was initially treated with alec-

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recovery (FLAIR)-hyperintense lesions were detected in the cortex (Fig. 1 E, F). These lesions gradually increased in size and number over the next year. Therefore, the patient was referred to our hospital. Before referral, the patient demonstrated no neurological symptoms, such as altered mental status, seizures, or focal neurological symptoms. Additionally, the lung and vertebral lesions were stable.

On admission, FLAIR MRI revealed miliary brain lesions with no gadolinium enhancement (Fig. 2). Some of the lesions were shown to be high density on computed tomography, which suggested calcification (Fig. 2). Blood testing showed the following results: white blood cell count - 7800/μL, hemoglobin - 14.8 g/dL, platelet count - 280,000/μL, C-reactive protein - 0.19 mg/dL, carcinoembryonic antigen - 122 ng/mL (< 4.9), cytokeratin 19 fragment - 8.7 ng/mL (< 2.0), and sialyl Lewis x antigen - 237 U/mL (< 38.0). An examination of the patient’s cerebrospinal fluid (CSF) revealed the following results: protein - 41 mg/dL, glucose - 64 mg/dL, cell count - 1/μL, carcinoembryonic antigen - 2.5 ng/mL, cancer antigen 19-9 - < 2.2 U/mL, cytokeratin 19 fragment - 1.3 ng/mL, and no cytological evidence of cancer dissemination. Bacterial, fungal, and mycobacterial cultures were all negative. The serum and CSF concentrations of brigatinib were 1039 ng/mL and 15.23 ng/mL, respectively.

Although the patient’s MRI findings were typical for miliary brain metastasis of lung cancer, it was unusual for the brain metastasis to progress when both the primary lung adenocarcinoma and the other metastatic lesions were responding to systemic therapy. Therefore, we performed a brain biopsy to determine whether the brigatinib treatment should be continued and to rule out other causes of the miliary brain lesions, such as infectious diseases (Lyme disease, C. albicans, Cryptococcus), primary central nervous system lymphoma, neurosarcoidosis, central nervous system vasculitis, Bechet’s disease, or unknown adverse effects caused by the brigatinib.

We biopsied the small area in the right frontal cortex that was indicated as high intensity on the FLAIR MRI and calcification on computed tomography. Hematoxylin and eosin staining revealed small clusters of tumor cells scattered in the perivascular space and cortex. The tumor cells did not show any characteristic structures. An immunohistochemical examination revealed that the tumor cells were positive for cytokeratin (CK) AE1/AE3, CK7, and thyroid transcription factor 1 and negative for CK20. ALK immunostaining revealed varying degrees of ALK positivity in the tumor cells, with some of the cells showing ALK negativity. Most of the ALK-positive cells were located within the perivascular space (Fig. 3).

The tumor was confirmed to be metastatic lung cancer on pathologic examination. Considering the characteristic MRI findings, a diagnosis of miliary brain metastasis was made. The patient was discharged, and another admission was scheduled for a whole-brain radiotherapy (WBRT) treatment. However, soon after discharge, the patient experienced a convulsive seizure and was readmitted. Since there was no improvement in the miliary metastatic lesions despite a sufficient brigatinib concentration in the CSF, the WBRT (37.5 Gy/15fr) was initiated during the emergency readmission. After the WBRT treatment, the brain lesions were nearly undetectable on an MRI (Fig. 1 G). We decided to continue the brigatinib therapy after the WBRT, as the lung and vertebral lesions were in remission, and the patient survived without progression for two years after the miliary brain metastasis was first detected.

3. Discussion

In this report, we describe a case of miliary brain metastasis of lung adenocarcinoma with isolated progression of the metastasis despite suppression of the primary lung lesion and vertebral metastasis with brigatinib therapy. The patient survived longer after successful WBRT than any other patients in previously reported cases.

While most miliary brain metastases occur during systemic cancer progression, our case is unique, in that tumor progression occurred only in the brain, and it occurred at a time when the other lesions were well-controlled. To the best of our knowledge, such a clinical course has not been reported previously. One possible reason for our findings is that the brain provides a good environment for tumor cells to survive. As reported previously, an important histological characteristic of miliary brain metastasis is that the tumor cells are located within the perivascular space (also known as the Virchow-Robin space). In contrast, other metastatic cells usually have a predilection for the gray-white

![Fig. 1. Timeline of treatment and response of primary lung and metastatic vertebral and brain lesions. A,B: T1- and T2- weighted images showing no lesions or gadolinium enhancement. C,D: Gadolinium enhancement and T2 hyperintensity in the left basal ganglia. E: Improvement in the T1- weighted gadolinium-enhanced lesion in the left basal ganglia. G: FLAIR image showing multiple cortical hyperintense lesions. CDDP: cisplatin, PEM: pemetrexed, BEV: bevacizumab, WBRT: whole brain radiotherapy, MRI: magnetic resonance imaging, FLAIR: fluid-attenuated inversion recovery.](image)
Fig. 2. Images obtained at four years from lung cancer diagnosis.
Upper row: Fluid-attenuated inversion recovery magnetic resonance image showing miliary brain lesions. Lower row: Computed tomography image showing partial calcification.

Fig. 3. A: Hematoxylin and eosin-stained brain biopsy specimen showing small clusters of tumor cells within the perivascular space. B: ALK-positive primary lung adenocarcinoma. C and D: ALK-stained metastatic tumor. C: ALK negativity. D: Heterogenous ALK staining. ALK: anaplastic lymphoma kinase.
matter junction, where there is sudden narrowing of the vascular diameter [7]. Although tumor cells may also be seen within the brain parenchyma in advanced miliary brain metastasis, normal histological structures, such as the blood-brain barrier, remain intact [4]. The peri-vascular space, where miliary metastatic cells are seen, is adjacent to, but isolated from the CSF pathway by leptomeningeal cells [9]. This may explain the progression of miliary brain metastasis in our patient despite a sufficient brigatinib concentration in the CSF. We believe that the WBRT treatment was effective because it penetrated the peri-vascular space, unlike brigatinib.

Our patient survived for more than two years after the detection of the miliary brain metastasis. This was significantly longer than the survival duration of weeks to months reported in previous cases. This was due to good systemic control of the disease with brigatinib and because of the significant effect of the WBRT. Although limited, there are reports of the use of WBRT for the treatment of miliary brain lesions, including two reports of patients with lung cancer. Both these patients showed regression of the miliary brain lesions; however, systemic disease progression resulted in only weeks to months of survival [3,6]. As in our case, patients with good systemic disease control could survive longer than those with inadequate systemic disease control. This might explain why patients with isolated progression of miliary brain metastasis can survive much longer than those with simultaneous miliary brain metastasis and systemic progression.

Herein, we have reported a case of an unusual clinical course of miliary brain metastasis in which isolated progression was observed despite good control of the systemic disease. A combination of WBRT and effective systemic treatment is a good strategy in such cases.

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Declaration of Competing Interest

None.

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