Focal Leptomeningeal Metastasis Following Curative Surgery for Lung Cancer
—Case Report—

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Abstract
A 58-year-old woman presented with 4 lesions of pulmonary adenocarcinoma which were curatively resected. No adjuvant therapy was needed because the lesions were all in the early stage. Magnetic resonance (MR) imaging of the brain, taken 10 months after the curative surgery, disclosed focal enhancement along the right central sulcus. Cerebrospinal fluid examination was normal. The lesion remained stable for 16 months, then began to spread out. She underwent open biopsy and the histological diagnosis was leptomeningeal metastasis from adenocarcinoma. She was treated with gefitinib at first because the lesion expressed epidermal growth factor receptor domain mutation. However, the lesion continued to enlarge, so she underwent whole cranial irradiation which was not effective. She died 2 years 10 months after the first detection of the metastasis. Early histological diagnosis is important even though the MR imaging lesion is not likely to be metastasis after curative surgery of the primary lesions.

Key words: focal lesion, leptomeningeal metastasis, lung cancer, biopsy

Introduction
Leptomeningeal metastasis occurs in 4–15% of cases of solid cancer and is one of the most important factors influencing the prognosis. The median survival is 8 weeks.17 Leptomeningeal metastasis can be diagnosed by the findings of cerebrospinal fluid (CSF) examination, although neuroimaging studies or clinical symptoms are helpful.4,18 Magnetic resonance (MR) imaging generally shows an extensive subarachnoid lesion. We describe a case of focal leptomeningeal metastasis without CSF abnormality which showed relatively slow progression, but was resistant to adjuvant therapy.

Case Report
A 58-year-old woman was introduced to our hospital because of abnormal lesions on chest roentgenography in September 2005. Chest computed tomography (CT) showed a mass lesion in the right lung indicating malignant tumor and 3 lesions of ground-glass opacity with diameters of 5 mm in the left lung. Brain CT screening for metastatic lesions did not show any abnormality. She underwent upper lobectomy of the right lung and the histological diagnosis was well differentiated adenocarcinoma. The other 3 lesions were not treated, because the patient did not accept the surgery immediately after the right lobectomy. She agreed to undergo the second surgery 10 months after the first surgery. The lesions were also diagnosed as well differentiated adenocarcinoma. No adjuvant therapy was needed because the pulmonary lesions were all in stage IA and curative surgery was performed. The lesions were thought to be independent, not intrapulmonary metastases.

Brain CT then disclosed a new focal enhanced lesion along the right parietal lobe (Fig. 1A), although the serum tumor markers for adenocarcinoma, carcinoembryonic antigen and cytokeratin fragment 19 (CYFRA), were negative. MR imaging showed the right central sulcus was enhanced with contrast medium (Fig. 1B). CSF examination showed no abnormal cancer-like cells, and glucose and protein levels were within normal limits. The brain lesion was considered to be possible focal leptomeningeal metastasis. According to the pulmonary surgeons’ opinion, the brain lesion was unlikely to be metastasis because the lung lesions were totally resected in the early stage. Moreover, the patient and her family hesitated to agree to open biopsy for the lesion because of possible post-operative hemiparesis. Therefore, the cerebral lesion was conservatively followed up with MR imaging. The lesion was slowly spreading out (Fig. 2A) and she began to feel numbness in the left hand. The cortex adjacent to the enhanced lesion appeared as low intensity on the T2-weighted image (Fig. 2B). She accepted surgery for histological diagnosis
Fig. 1 A: Brain computed tomography scan with contrast medium in August 2006 showing a high density area in the parietal lobe. B: T1-weighted magnetic resonance image with gadolinium showing linear enhancement in the central sulcus (arrows).

Fig. 2 A: Preoperative T1-weighted magnetic resonance image with gadolinium in December 2007 showing enlargement of the enhanced lesion. B: Magnified view of the preoperative T2-weighted magnetic resonance image showing a low intensity lesion in the cortex adjacent to the lesion.

Fig. 3 Photomicrographs showing tumor cells filling up the subarachnoid space (arrows) and invading into the brain parenchyma. Red blood cells are seen around the tumor cells. Hematoxylin and eosin stain, ×100 (A), ×400 (B).

Fig. 4 T1-weighted magnetic resonance images with gadolinium in December 2008 showing more enlargement of the enhanced lesion and the perifocal low intensity area indicating invasion.

of the cerebral lesion in January 2008.

The dura was intact, but the arachnoid membrane was diffusely thickened. The brain surface was partly yellowish. The specimen was taken from the extended lesion in the right parietal lobe to prevent injury to the motor cortex. Histological examination revealed that the tumor cells had filled the subarachnoid spaces and also the Virchow-Robin spaces, so invading into the parenchyma (Fig. 3A). In addition, red blood cells were sparsely seen around tumor cells (Fig. 3B). The diagnosis was metastatic adenocarcinoma originating from the lung cancer. Follow-up chest CT just after this diagnosis showed recurrence of the mass lesion.

The epidermal growth factor receptor (EGFR) domain mutation was expressed in the surgical specimen, so the adenosine triphosphate-competitive inhibitor of EGFR gefitinib was expected to be effective. She was at first treated with gefitinib instead of irradiation. However, she gradually showed additional neurological deficits of mild left hemiparesis and sensory disturbance in the left hand. She had visual epilepsy and simple partial seizures of the left hand once a week. The lesion was remarkably enlarged in spite of chemotherapy (Fig. 4), though the recurrent pulmonary lesion disappeared. Six months later, she underwent whole cranial irradiation (40 Gy) which was ineffective. She died 2 years and 10 months after the first detection of the brain lesion on CT without recurrence of the primary lesions or any other metastasis.
Discussion

Metastatic brain tumor accounts for about 10% of cancer cases, and the most common primary lesion is lung cancer.\(^{11,12}\) The median survival period of metastatic brain tumor is about 6 months. In contrast, leptomeningeal metastasis occurs in 4–15% of all solid malignant tumors and the median survival period is about 8 weeks,\(^ {17}\) and the common primary lesions are breast cancer, lung cancer and melanoma.\(^ {7}\) Among patients with leptomeningeal metastasis, 82% already had metastasis besides intracranial lesions and 16% had only brain metastasis at the diagnosis of leptomeningeal metastasis. Only 3.5% of the patients developed leptomeningeal metastasis without any other metastasis. A total of 44% of patients showed leptomeningeal metastasis within a year from the diagnosis of the primary site.\(^ {17}\)

Leptomeningeal metastasis can be identified with CSF findings, but MR imaging is also useful.\(^ {4,18}\) Typical findings of leptomeningeal metastasis on MR imaging are diffuse contrast enhancement of the meninges and subarachnoid masses.\(^ {3,7}\) Ventricular dilation also occurs due to CSF absorption failure. Our case showed leptomeningeal enhancement on MR imaging, but the lesion was quite limited in the right central sulcus. Tumor nodules were not found by MR imaging or in the surgical specimen. In addition, no CSF abnormality was disclosed. The histological specimen showed tumor cells in the subarachnoid space invading diffusely into the Virchow-Robin spaces and parenchyma. Such findings indicate that the lesion was focal leptomeningeal metastasis. The surface of the cortex adjacent to the affected sulci appeared as low intensity on \( T_2\)-weighted MR imaging. The origin of this low intensity is unknown, but may be congestion or tumor cells invading into the parenchyma. The lesion showed very slow progression, especially in the earlier period, but became more aggressive once spreading out began. The patient did not show any symptoms or neurological deficits for the first 16 months after the first detection of the CT abnormality. Ultimately, the patient survived for 2 years 10 months without response to treatment. This type of metastasis has a completely different clinical course and neuroimaging appearance compared to the more usual findings of leptomeningeal metastasis.

The EGFR inhibitor gefitinib is effective against intracranial metastatic adenocarcinoma in general.\(^ {10,11,15,16}\) Overall disease control rate was 27–63% and the median progression free survival was 3.0–5.0 months.\(^ {2,3,9}\) and gefitinib may be effective against leptomeningeal metastasis.\(^ {1,6,13}\) Our patient was first treated with gefitinib because mutation of EGFR domain was observed. However, in contrast to the disappearance of the recurrent pulmonary lesions, the brain lesion continued to enlarge. Then radiation therapy was started, but was not effective. Leptomeningeal metastasis cannot be treated surgically, so early detection and treatment of the lesion may lead to a better prognosis. Systemic chemotherapy may be effective,\(^ {8}\) but irradiation is the most effective and reliable treatment for leptomeningeal metastasis at the present.

MR imaging in this case did not show typical leptomeningeal metastasis, and no tumor cells were found in the CSF. Since the 4 independent primary lesions were all in the early stage and totally removed, brain metastasis could scarcely occur. As a result, the correct diagnosis was delayed. Positron emission tomography is useful to detect unexpected distant metastasis.\(^ {5,14}\) We emphasize the importance of histological diagnosis as soon as possible when the suspected metastatic lesions are identified even though curative surgery for primary lesions has been performed.

References

cose positron emission tomography in the detection of dis-
tant metastases of non-small-cell lung cancer. Clin Lung Can-
15) Sugio K, Uramoto H, Ono K, Oyama T, Hanagiri T, Sugaya M, Ichiki Y, So T, Nakata S, Morita M, Yasumoto K: Mu-
tations within the tyrosine kinase domain of EGFR gene spe-
cifically occur in lung adenocarcinoma patients with a low
16) Uramoto H, Sugio K, Oyama T, Ono K, Sugaya M, Yoshimatsu T, Hanagiri T, Morita M, Yasumoto K: Epider-
mal growth factor receptor mutations are associated with
gefitinib sensitivity in non-small cell lung cancer in
17) Waki F, Ando M, Takashima A, Yonemori K, Nokihara H,
Miyake M, Tateishi U, Tsuta K, Shimada Y, Fujiwara Y,
Tamura T: Prognostic factors and clinical outcomes in
patients with leptomeningeal metastasis from solid tumors. J
Neurooncol 93: 205–212, 2009
18) Yousem DM, Patrone PM, Grossman RI: Leptomeningeal
metastasis: MR evaluation. J Comput Assist Tomogr 14:
255–261, 1990

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