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Significance of an epidermal growth factor receptor mutation in cerebrospinal fluid for leptomeningeal metastasis and successful treatment with osimertinib: A case report and literature review

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Dear Editor

Leptomeningeal metastasis (LM) is associated with poor prognosis; in cases of LM from non-small cell lung cancer (NSCLC), an improvement in prognosis can be expected if molecular targeted drugs are available. Gefitinib, a first-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), and erlotinib, a second-generation EGFR-TKI, are more effective than conventional treatment for LM from EGFR-mutation-positive NSCLC [1]. Moreover, osimertinib, a third-generation EGFR-TKI with good central nervous system penetration, is more effective for treating LM from EGFR mutation-positive NSCLC [2,3]. Therefore, it is important to determine whether osimertinib can be used in the treatment of LM. We report a case of LM where detecting an EGFR mutation in the cerebrospinal fluid (CSF) was useful in the diagnosis and treatment of lung cancer and review the related literature.

A 60-year-old man presented with a 2-month history of weight loss, anorexia, and headache and an 18-day history of disorientation and hallucination. His medical history included hypertension and a 40-pack year smoking history. Neurological examination revealed disturbed consciousness, terminal tremor in his left arm, and mild neck stiffness. Laboratory data showed elevated serum and CSF CYFRA levels, mild pleocytosis, elevated protein levels, and decreased CSF glucose levels. Gadolinium-enhanced T1-weighted brain magnetic resonance imaging (MRI) revealed hydrocephalus, diffuse leptomeningeal enhancement, and small enhanced lesions in the right basal ganglia and left frontal subcortical white matter (Fig. 1A-B). CSF cytology revealed the presence of malignant cells (Fig. 1C-D); therefore, we diagnosed LM. Chest computed tomography showed a nodular infiltrative shadow on the mediastinal side of the right S6 (Fig. 1E-F), and 18F-fluorodeoxyglucose-positron emission tomography revealed accumulation in the lesion and bony metastases in the vertebral body of Th3 and the pelvis (Fig. 1G). To diagnose the primary lesion, he underwent bronchoscopy, including needle biopsy and lavage cytology of the lesion, but a specimen from the lesion could not be collected because of difficulty in accessing the tumor; lavage cytology produced negative results. Surgical biopsy was considered difficult because of the patient's poor condition. Therefore, we investigated EGFR mutations using the CSF. An E746-A750 deletion (2235–2249) was found in exon 19. We thus diagnosed LM from EGFR mutation-positive NSCLC. We treated him with osimertinib orally, 80 mg per day; his consciousness and anorexia markedly improved over a few days. Gadolinium-enhanced T1-weighted brain MRI 7 months after treatment initiation revealed continued improvement with decreasing enhancement of leptomeningeal and nodal lesions (Fig. 1H-I). He received continuous treatment thereafter and experienced no exacerbation for over 500 days.

LM has a poor prognosis; in NSCLC, it is approximately 1–3 months [1]. However, in patients with EGFR mutation-positive NSCLC with central lesions, first-line treatment with osimertinib results in a median progression-free survival of ≥27 months [2]. A similar effect is seen against LM [2,3]. Compared with previous chemotherapy regimens, this regimen results in a significant improvement in prognosis; therefore, an accurate diagnosis is important for deciding on osimertinib use. The diagnostic procedure comprises genetic testing, including that for EGFR mutations, using a biopsied specimen of lung cancer. However, if bronchoscopic or surgical biopsy is difficult due to tumor location or poor general condition (e.g., older age, presence of LM), genetic testing cannot be performed, and there may be no choice but to select palliative treatment. In our case, we could administer osimertinib because an EGFR mutation was identified using a CSF sample. This allowed treatment that led to a rapid improvement in LM and a significant improvement in prognosis; thus, genetic testing of CSF for EGFR mutations can be useful in determining treatment strategies. Regarding LM from NSCLC, there are some reports that genetic testing for EGFR mutations using CSF is useful [4–8]. Shingyoji et al. [5] reported that in patients with LM from NSCLC, CSF cytology and CSF EGFR mutations using direct DNA sequencing had similar detection rates of 45%. Additionally, Sasaki et al. [6] reported that in patients with LM from EGFR mutation-positive NSCLC, a comparison of the detection rates between CSF cytology and CSF EGFR mutation using real-time polymerase chain reaction (PCR) revealed that the sensitivity of CSF EGFR mutation was higher (CSF cytology 2/7 [28.6%], CSF EGFR mutation 7/7 [100%],

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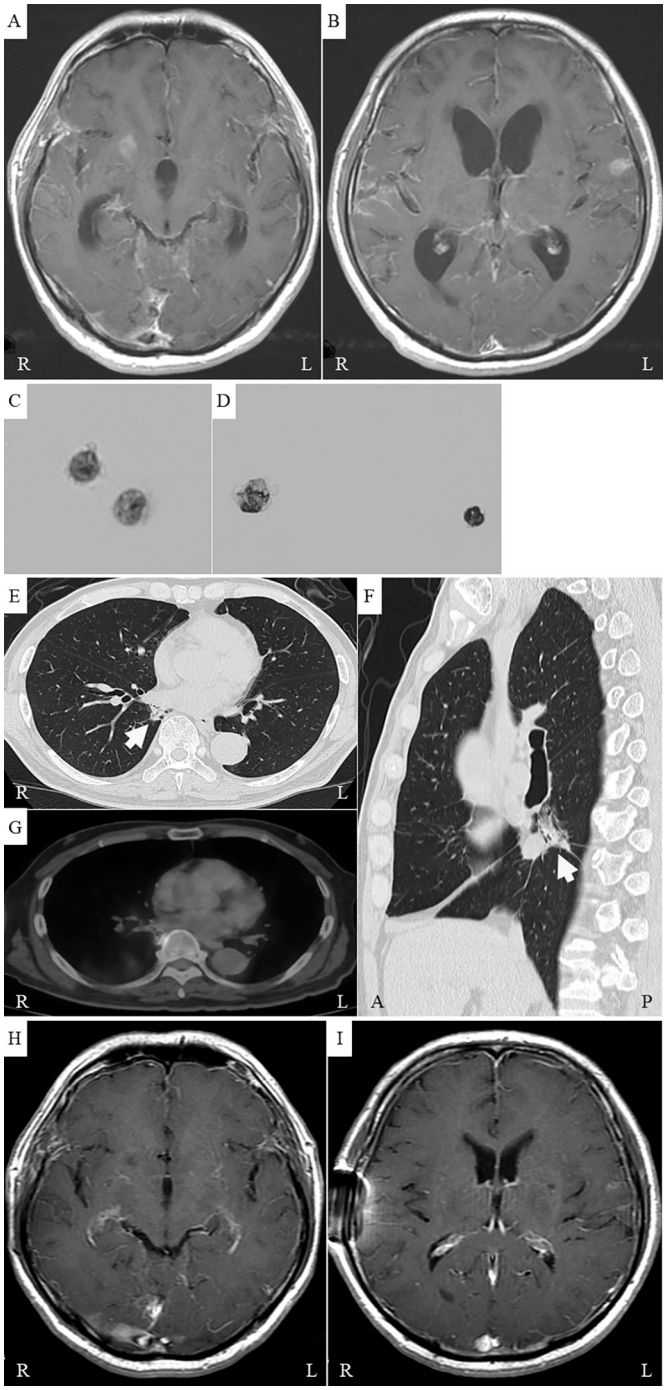

Fig. 1. Gadolinium-enhanced T1-weighted brain magnetic resonance imaging (MRI) revealed hydrocephalus, diffuse leptomeningeal enhancement, small enhanced lesions in the right basal ganglia and left frontal subcortical white matter (A-B). Papanicolaou (C) and Giemsa (D) staining of cells in the CSF revealed a high N/C ratio, irregularly shaped nuclei, anisokaryosis, and prominent nucleoli. Chest computed tomography shows a nodular infiltrative shadow on the mediastinal side of the right S6 (E-F), and 18F-fluorodeoxyglucose-positron emission tomography revealed accumulation in the lesion (G). Gadolinium-enhanced T1-weighted brain MRI 7 months after treatment initiation revealed continued improvement with decreasing enhancement of leptomeningeal and nodal lesions (H-I).

serum EGFR mutation 0/3 [0%]). Moreover, Li et al. [7] reported that in patients with LM from EGFR mutation-positive NSCLC, EGFR mutations in CSF could be detected with greater sensitivity using next-generation sequencing (cytology 18/28 [64.3%], CSF EGFR mutation 26/26 [100%], and serum EGFR mutation 19/26 [73.1%]). In patients with LM from NSCLC, a comparison between lung cancer biopsy samples and CSF for detecting EGFR mutations using amplification-refractory mutation system PCR showed a high concordance rate (93.6%) [8]. Thus, detection of EGFR mutations in the CSF is especially useful for diagnosing LM from NSCLC. However, if next-generation sequencing becomes generally available, genetic blood tests may become easier, although the sensitivity is slightly lower. EGFR mutation-positive NSCLC is more likely to cause LM than EGFR mutation-negative cancer, with LM occurring in 9.4–30.8% of mutation-positive cases [9,10]. Therefore, genetic testing of CSF is worthwhile when a primary lung cancer sample cannot be tested. EGFR mutations are highly specific to lung cancer and are rarely found in other cancers. Therefore, even in cases of LM that have a small lung lesion or when biopsy is difficult to perform, identification of an EGFR mutation in the CSF is also useful for clearly identifying the lung cancer as the primary cancer. Regarding osimertinib treatment, improvement occurred within 15 days of osimertinib initiation in 25% of patients [3], as in our case. In general, patients are treated with osimertinib alone, and its combination with radiotherapy or chemotherapy has yet to be established [1]. The most frequent side effects of osimertinib include diarrhea, dry skin, decreased appetite, and headache.

In conclusion, if a patient is suspected of having LM from NSCLC with a difficult to diagnose primary lesion, detecting EGFR mutations in CSF, which is relatively easy, is useful when deciding on the diagnosis and treatment of lung cancer. Significantly improved prognosis can be expected following treatment with a molecular targeted drug.

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Takeo Sakurai[a,*], Akimasa Tuchida[b], Hiroshi Nishida[a]
[a] *Department of Neurology, Gifu Prefectural General Medical Center, Gifu, 4-6-1 Noisshiki, Gifu 500-8717, Japan*
[b] *Department of Respiratory Medicine, Gifu Prefectural General Medical Center, Gifu, 4-6-1 Noisshiki, Gifu 500-8717, Japan*

[*] Corresponding author.
E-mail addresses: takeo-sakurai@gifu-hp.jp (T. Sakurai), hi-nishida31@gifu-hp.jp (H. Nishida).