Case Report

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Cerebrospinal fluid tumor markers predict treatment response in a patient with carcinomatous meningitis

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Abstract

We report on a 56-year-old female patient diagnosed with carcinomatous meningitis caused by lung cancer. The diagnosis was confirmed by lung computed tomography, enhanced brain magnetic resonance imaging, histopathology, cerebrospinal fluid (CSF) cytology, and serum and CSF tumor markers. Genetic testing detected an epidermal growth factor receptor gene exon 19 deletion. The patient survived for 29 months after systemic treatment with gefitinib, radiotherapy, and chemotherapy. Dynamic monitoring of CSF and serum tumor markers was carried out during the treatment process. We considered that CSF tumor marker levels may have allowed the early diagnosis of meningeal carcinomatosis, and that systemic therapy in the early stage of the disease may prolong survival.

Keywords

Carcinoembryonic antigen, carbohydrate antigen125, CYFRA21-1, meningeal carcinomatosis, tumor marker, cerebrospinal fluid

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Introduction

Meningeal carcinomatosis (MC) is a malignant cancer of the nervous system. The most common primary cancers associated with MC include breast and lung carcinomas, lymphoma, and leukemia.[1] The prognosis of MC is very poor, and patients with

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untreated MC may only survive for a few weeks. We therefore need to explore new methods for diagnosing early-stage MC, as well as effective treatments aimed at prolonging life expectancy.

There is currently no reliable method for assessing treatment response in patients with MC. Neurological evaluation and cerebrospinal fluid (CSF) cytology examination do not provide useful information in early-stage MC. However, tumor marker levels, especially in the CSF, may aid the diagnosis of MC and help to evaluate treatment response in patients with early-stage disease. We report the case of a patient with MC who received systemic treatment in the early stage and survived for almost 29 months.

Case report

A 56-year-old woman was admitted with a 1-month history of persistent headache, initially localized to the right temple but gradually spreading to the whole cranium. No nausea or vomiting was reported. Fundus examination showed bilateral papilledema, and no other positive signs on neurological examination. Lumbar puncture suggested high intracranial pressure (230 mmH_2O), and routine CSF and biochemical tests showed no abnormalities. Levels of CSF tumor markers, including carbohydrate antigen 125 (CA125 1514 IU/mL), CYFRA21-1 (55.11 μg/L), and carcinoembryonic antigen (CEA 3478 μg/L) were significantly above normal levels. However, CA153, CA199, CA724, neuron-specific enolase, alpha-fetoprotein, and squamous cell carcinoma antigen (SCC) levels were within the normal ranges, and the results of CSF cytology examination were negative. Lung computed tomography (CT) suggested right lung cancer (Figure 1a), and the pathological diagnosis was adenocarcinoma. Enhanced brain magnetic resonance imaging (MRI) revealed extensive soft meningeal enhancement (Figure 1b, 1c). The final diagnosis was MC. Genetic testing detected an epidermal growth factor receptor gene (*EGFR*) exon 19 deletion.

Initial treatment involved whole-brain radiotherapy (40 Gy/20 times) and targeted therapy (gefitinib 0.25 g per day). CSF and serum tumor markers were tested regularly. Atypical cells with increased cytoplasm and mitotic activity were detected by CSF cytology examination in the third week (Figure 1d).

The patient's headache symptoms failed to improve by the fourth week, and she experienced occasional nausea and vomiting. At that time, laboratory results suggested that her serum CEA and CA125 levels had declined, while the CSF CA125 and CYFRA21-1 results remained the same. Considering the patient's worsening clinical symptoms, we added intrathecal chemotherapy (methotrexate 5 mg and nimotuzumab 50 mg per week, 9 times). By the sixth week, the patient's headache had improved and her nausea and vomiting had ceased. Her CSF tumor marker levels decreased significantly after systemic therapy. By the eighth week, CSF cytology detected no atypical cells, and by the ninth week, the patient's headache had completely resolved.

The patient's clinical symptoms worsened again in week 64. Her symptoms of nausea and vomiting reappeared, and she had difficulty walking and showed psychomotor retardation. Brain MRI showed extensive soft meningeal enhancement, CSF tumor marker levels were increased, and atypical cells were again found in the CSF. In addition to gefitinib, we immediately restarted intrathecal chemotherapy (methotrexate 10 mg and nimotuzumab 50 mg per week, 6 times). The patient's condition gradually stabilized in week 68, with only mild headache, decreased CSF tumor marker levels, and no atypical cells.

In week 101, the patient experienced severe headache, vomiting, impaired vision, and lethargy. However, CSF and serum

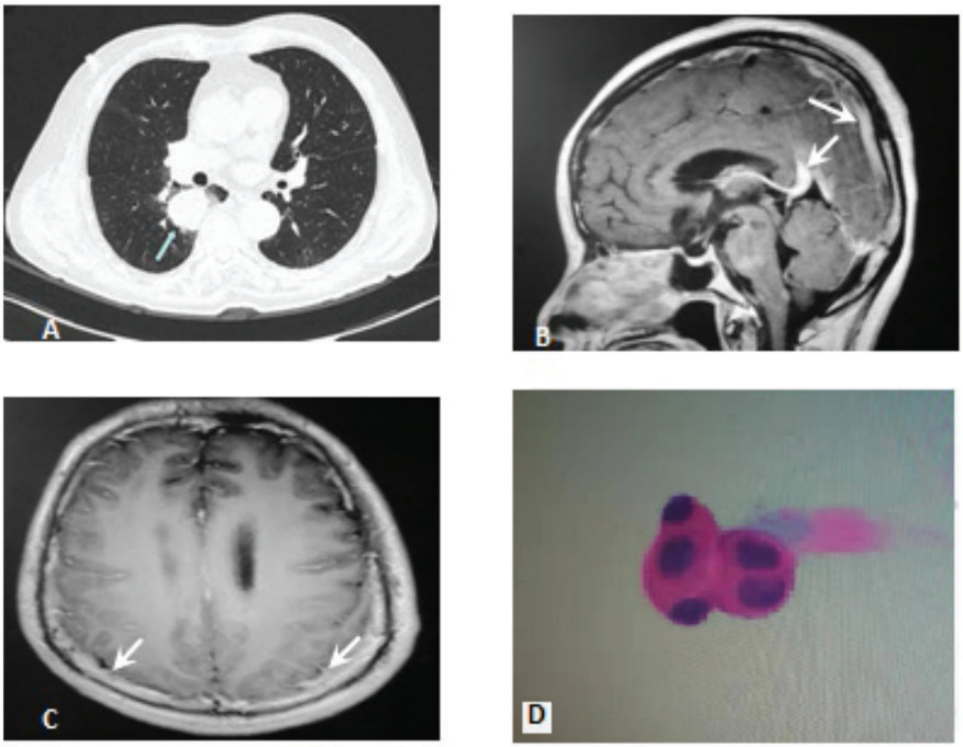

Figure 1. Imaging examinations. (a) Lung computed tomography revealed right lung cancer (arrow). (b, c) Brain magnetic resonance imaging suggested extensive soft meningeal enhancement (arrow). (d) Atypical cells were detected by cerebrospinal fluid cytology examination. (Hematoxylin–eosin stain, ×200).

tumor marker levels were not further elevated. Her symptoms were not relieved by intrathecal treatment. Serum tumor marker levels increased rapidly in week 110 and the patient eventually died in week 113.

We monitored the dynamic changes in CA125, CEA, and CYFRA21-1 levels throughout the course of the patient's illness and treatment (Figures 2, 3, and 4). However, CA153, CA199, CA724, NSE, AFP, and SCC levels fluctuated within their normal ranges throughout the course.

The patient provided signed consent for publication of this report.

Discussion

Previous studies indicated that MC occurred in 3% to 5% of cancer patients, characterized by clinical neurological symptoms.[2] The typical clinical symptoms of MC include headache, vomiting, papilledema, increased intracranial pressure, and positive Kernig sign; however, specific clinical manifestations are unfortunately lacking.[3–5] MC is a serious and late complication of malignant tumors, with an extremely poor prognosis and a median survival time of only 4 to 6 weeks if left untreated.[6]

The current patient suffered non-specific headache symptoms on admission to hospital, which could easily be misdiagnosed. Although the results of CSF cytology examination were negative, we diagnosed MC based on CSF tumor marker levels and imaging findings. Tumor markers, including CEA, CA125, and CYFRA21-1, are mainly produced by tumor-reactive

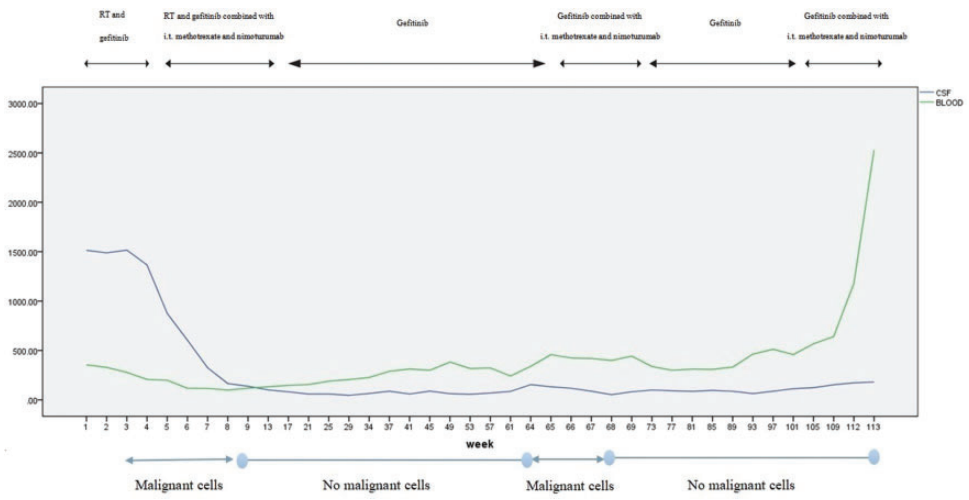

Figure 2. Dynamic analyses of cerebrospinal fluid and serum CA125 levels.
RT, radiotherapy; i.t., intrathecal; CSF, cerebrospinal fluid.

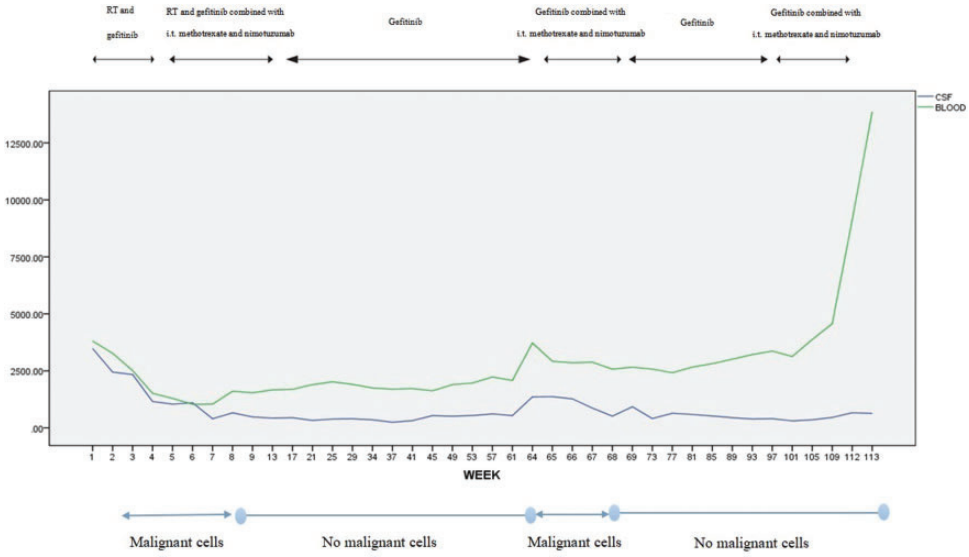

Figure 3. Dynamic analysis of cerebrospinal fluid and serum CEA levels.
RT, radiotherapy; i.t., intrathecal; CSF, cerebrospinal fluid.

substances and thus reflect the existence and severity of the tumor.[7] The healthy nervous system does not produce CEA, and high levels of CEA in the CSF thus strongly suggest MC. Notably, a remarkable feature of this case was the high CSF level of CYFRA21-1, which was 20 times higher than the level of serum CYFRA21-1 at the time of first lumbar puncture, thus supporting the diagnosis of MC.

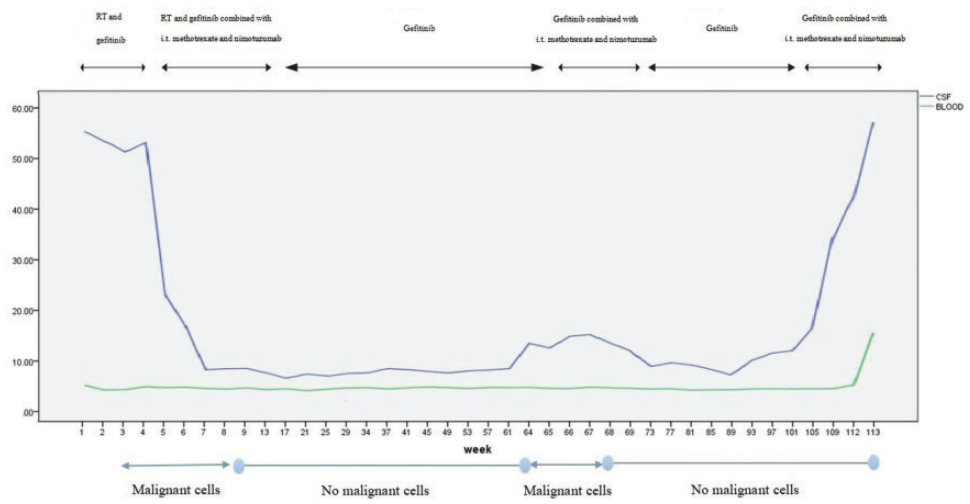

Figure 4. Dynamic analysis of cerebrospinal fluid and serum CYFRA21-1 levels.
RT, radiotherapy; i.t., intrathecal; CSF, cerebrospinal fluid.

At the beginning of treatment, serum levels of CA125 and CYFRA21-1 decreased gradually, while CSF levels showed no significant decline. Meanwhile, the patient's clinical neurological symptoms worsened, and did not improve until the CSF tumor marker levels decreased. We therefore considered that CSF tumor markers may predict treatment response in patients with early-stage MC, and a significant decline in CSF tumor marker levels may indicate a better prognosis.

Regarding the treatment of the current patient, we considered that early radiotherapy might have been an important factor affecting her long-term prognosis. To some extent, meningeal metastasis indicated that the blood–brain barrier had been partially destroyed, and early combined radiotherapy may have further increased the drug permeability in the central nervous system.

Intrathecal chemotherapy is widely used for the treatment of meningeal metastases,[8] and can prolong patient survival compared with palliative treatment alone.[9] During treatment of the current patient, CSF cytology became negative after intrathecal chemotherapy and remained negative for a prolonged period. The main complications of intrathecal chemotherapy are infection and obstruction of the CSF circulation; however, neither of these complications occurred in this patient. We therefore considered that intrathecal chemotherapy was a safe and effective method for the treatment of MC.

In this case, gefitinib was an effective long-term treatment for MC; however, the addition of intrathecal chemotherapy may help when the patient's clinical symptoms worsen or atypical cells appear in the CSF. Gefitinib is an EGFR A–tyrosine kinase inhibitor. Although pre-clinical studies showed that gefitinib was rarely distributed in mouse brain tissues, it has demonstrated an inhibitory effect on brain metastases in clinical trials.[10,11] Sudo et al. reported that gefitinib could achieve a stable disease rate of 60% in patients with MC caused by lung cancer, and its side effects were mostly tolerable.[11] Targeted drugs such as gefitinib were shown to alleviate symptoms and prolong survival in

patients with lung adenocarcinoma with *EGFR* gene mutation.[12]

In summary, the current case suggests that long-term survival of patients with MC may be associated with an early diagnosis, *EGFR* exon 19 deletion, combined systemic treatment, and regular monitoring.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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