Malignant Meningitis Secondary to Lung Adenocarcinoma: An Unusual Relapse

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Abstract

We describe a 64-year-old man with locally advanced lung adenocarcinoma who had meningeal relapse soon after the completion of intensive chemo-radiotherapy. Diagnosis of the malignant meningitis was established by cytological examination of the cerebrospinal fluid, which showed malignant cells consistent with adenocarcinoma from the primary site. Although very rare, it is possible that successful chemo-radiotherapy for locally advanced lung cancer could not prevent malignant meningitis as observed in our patient. Physicians should consider performance of brain MRI or contrast CT of the brain and a lumbar puncture to exclude the diagnosis of malignant meningitis, an uncommon but devastating complication of malignancy.

Key words: malignant meningitis, chemo-radiotherapy, lung cancer, recurrence

Introduction

Non-small cell lung cancer (NSCLC) presents in an advanced stage in three-fourths of patients but one-third of the disease is confined within thorax. The advent of concurrent chemo-radiotherapy has improved the survival of these locally advanced NSCLC patients, although the 5-year survival rate is only 15% (1). We report herein a case with the unusual recurrence of malignant meningitis in spite of soon after the completion of concurrent chemo-radiotherapy.

Case Report

A 64-year-old man who had a 3-month history of productive cough was admitted to our division. Physical examination was unremarkable, except for enlarged lymph nodes in the left supraclavicular fossa. Chest radiography and CT scan showed a 5 cm mass in left upper lung and mediastinal lymphadenopathy (Fig. 1). The serum carcinoembryonic antigen (CEA) level was elevated at 348.3 ng/ml. A biopsy of a lymph node was taken for histological evaluation. The polygonal tumor cells proliferated diffusely and formed solid nests. Although there were no glandular or papillary structures in the tumor, many tumor cells contained abundant mucin in their cytoplasms. Immunohistochemically, the tumor cells showed a diffusely positive reaction for thyroid transcription factor-1. According to the findings, the tumor was diagnosed as a poorly differentiated adenocarcinoma, and the lung was highly suspected to be the primary site of the tumor. Examination by systemic survey revealed no metastases. Therefore, the patient was diagnosed as having lung adenocarcinoma with clinical-T2N3M0 stage IIIB. Performance status (ECOG) of the patient was 1, and he was treated with concurrent chemo-radiotherapy using a combination of cisplatin (80 mg/m², day 1) and vinorelbine (25 mg/m², day 1 and 8) every 4 weeks. Thoracic irradiation (66 Gy in 33 fractions of 2 Gy once daily, day 1 to 68) was performed concurrently. Grade 3 hematological side-effects were observed; however, the patient tolerated this treatment and had a good partial response (Fig. 2). Follow-up brain MRI showed no brain metastasis. The CEA level returned to 45.0 ng/ml.

Unfortunately, 3 weeks after completion of the chemo-radiotherapy, he developed nausea and vomiting, and also complained of dizziness and gait disturbance. At that time, his neck did not show apparent meningismus. The patient was alert and oriented, but his gait was becoming worse. Al-
though there was no brain metastasis on brain MRI which was performed 3 weeks earlier, a diagnosis of malignant meningitis was suspected, thus a CT of the brain with intravenous contrast and a lumbar puncture was carried out. CT of the brain revealed hydrocephalus and contrast enhancement of the cerebral sulci (Fig. 3). Cytological examination of the cerebrospinal fluid showed malignant cells consistent with the original lung adenocarcinoma (Fig. 4). Although dexamethasone and glycerin were administered intravenously, the patient’s general condition deteriorated rapidly, precluding him from further treatment. He died 3 weeks later. Post-mortem examination was declined.

**Discussion**

Lung cancer is one of the most common cancers in men. Metastases usually occur in the mediastinal lymph node, bone, and lung. Less commonly, they occur in brain and liver. There are some reports of meningeal relapse in lung cancer (2-4). The development of malignant meningitis as the sole manifestation of cancer is unusual and most cancer patients have active systemic disease.

![Chest CT scan on admission](image1)
**Figure 1.** Chest CT scan on admission showed a 5 cm mass in the left upper lung and mediastinal lymph adenopathy.

![Chest CT scan after chemo-radiotherapy](image2)
**Figure 2.** Chest CT scan after the chemo-radiotherapy revealed shrinkage of the primary lesion and mediastinal lymphadenopathy, which was evaluated as a good partial response.

![CT of the brain](image3)
**Figure 3.** CT of the brain 3 weeks after completion of the chemo-radiotherapy revealed hydrocephalus and contrast enhancement of the cerebral sulci.

![Cytological examination](image4)
**Figure 4.** Cytological examination of the cerebrospinal fluid showed malignant cells (A) (×400, Papanicolaou stain) consistent with the original lung adenocarcinoma (B)(×200, Hematoxylin-Eosin stain).
Carcinomatous meningitis occurs in approximately 5 to 18% of lung cancer patients (5, 6). The most frequently involved histological types are small cell lung cancer and adenocarcinoma. Carcinomatous meningitis might be increasingly diagnosed as anticancer therapies become more effective and result in prolonged survival. The use of better neuroimaging techniques also may contribute to a higher rate of detection. In patients with advanced breast cancer, Kosmas et al reported isolated leptomeningeal carcinomatosis after taxane-induced major remission (7). They showed that 7 of 155 patients developed leptomeningeal carcinomatosis as the first evidence of progression after taxane-based regimens with a median interval of 6 months (7). Omuro et al recently reported high incidence of disease recurrence in the brain and leptomeninges in patients with non-small cell lung carcinoma after response to gefitinib (8). The present patient was evaluated as having a good partial response, therefore, his sudden deterioration needed to be explained. We supposed that cancer cells might have spread by infiltration through the arachnoid vessels or choliid plexus following hematogenous or lymphatic dissemination, despite the intensive concurrent chemo-radiotherapy.

Malignant meningitis is the diffuse involvement of leptomeninges infiltrating malignant cells. The most common primary malignancies associated with this condition include lung cancer, breast cancer, melanoma, and the lymphomas (9, 10). Signs and symptoms of malignant meningitis depend on which part of the neuroaxis is seeded. Cerebral involvement may present with headache, change in mental status, and persistent nausea and vomiting. Therefore, the diagnosis of malignant meningitis may not be easily recognized. Although identification of malignant cells in the cerebrospinal fluid is diagnostic, initial tests may be falsely negative in up to 50% of patients with malignant meningitis (11). Therefore, when a diagnosis of malignant meningitis is suspected, a brain imaging study should be performed first. MRI is the preferred imaging study. If MRI is not immediately available, a CT of the brain with intravenous contrast should be performed before lumbar puncture. Abnormalities include hydrocephalus and contrast enhancement of the cerebral sulci or cistern on contrast-enhanced CT scan (10). However, the contrast-enhanced CT scan may be normal in 18% to 44% of patients with malignant meningitis (10, 12).

Penetration of the central nervous system (CNS) is poor with most drugs, even with intensive high-dose chemotherapy. The Southwest Oncology Group study showed that the median survival, even in patients who responded to treatment, was only 5.7 months and that non-responders had a survival of 1.8 months (13). Survival in these patients ultimately remains very poor and there is a need for new drugs and approaches to treatment.

Malignant meningitis is a particularly devastating complication, especially after the successful treatment of disease elsewhere in the body (14). Although very rare, it is possible that successful chemo-radiotherapy for locally advanced NSCLC patients could not prevent meningeal relapse as observed in our patient, because CNS is a potential sanctuary site. In a patient with a history of malignancy, nausea and vomiting may be the first sign of CNS involvement. Therefore, physicians should consider contrast CT of the brain or MRI and a lumbar puncture to exclude the diagnosis of malignant meningitis, an uncommon but devastating complication of malignancy.

References


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