Complete response of 7 years' duration after chemoradiotherapy followed by gefitinib in a patient with intramedullary spinal cord metastasis from lung adenocarcinoma

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ABSTRACT Intramedullary spinal cord metastasis is a rare but serious complication which causes rapid progression of neurological deficits. Here we report a 35-year-old man presenting with increasing leg pain and gait disturbance, 8 months after surgery for lung adenocarcinoma. Spinal magnetic resonance imaging revealed an intramedullary tumor at the Th7/8 level. Radiotherapy at 35 Gy resulted in transient symptomatic improvement, but during chemotherapy with vinorelbine and cisplatin, symptoms worsened again. Gefitinib was then administered; the patient improved after 2 weeks and has now maintained a complete response for 7 years.

KEY WORDS Intramedullary spinal cord metastasis; lung cancer; gefitinib; EGFR; magnetic resonance imaging; positron-emission tomography

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Introduction

Intramedullary spinal cord metastasis (ISCM) is a rare but serious cancer complication which causes rapid progression of neurological deficits within a period of days to weeks (1-3). Prognosis is poor, with median survival of 4 months (4). Optimum treatment remains controversial. Here we report a patient with ISCM from lung adenocarcinoma, in whom chemoradiotherapy followed by gefitinib was effective for 7 years.

Case report

A 35-year-old man underwent a right lower lobectomy in March 2005. He had a smoking history of 15 pack-years. Resected specimens revealed adenocarcinoma, mixed subtypes, bronchioloalveolar > acinar, measuring 2.5-cm in size with 2 nodules of intrapulmonary metastases in the same lobe (Figure 1). The pathological stage was IIB, pT3N0M0 (5). Serum carcinoembryonic antigen (CEA) levels were slightly increased to 9.4 ng/dL, then normalized following surgery. Two cycles of postoperative adjuvant chemotherapy with docetaxel and carboplatin were implemented.

In November, 2005, the patient reported numbness extending from the right hip to the toes upon awakening, which developed into pain in both legs the next day. On admission, sensory disturbance of Th10 or lower was observed. Magnetic resonance imaging (MRI) revealed an intramedullary spinal cord tumor at Th7/8, showing a high-intensity area with fusiform bulging in T2-weighted images and a gadolinium-enhanced core in T1-weighted images (Figure 2A,B). Positron emission tomography, serum CEA level and cerebrospinal fluid cytology were all negative. Surgical resection was offered but rejected. The symptoms progressed further and urinary incontinence began two weeks later. Gait disturbance occurred due to reduced tendon reflexes.

In December 2005, treatment was initiated with high dose steroids, followed by concurrent chemoradiotherapy consisting of irradiation (35 Gy in 13 fractions), vinorelbin and cisplatin.

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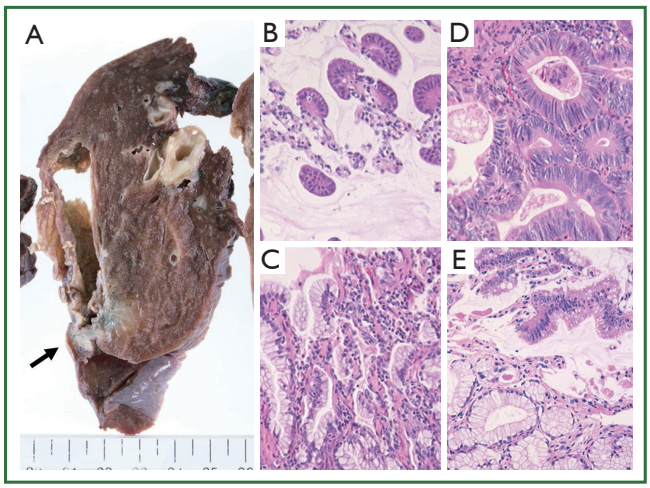

Figure 1. Resected right lower lobe. A. Resected specimen showing irregular nodule, 2.5-cm in size, arising in the cyst wall; B-D. Histological examination of the nodule revealing adenocarcinoma, mixed subtypes, bronchioloalveolar > acinar; E. Histological examination of the intrapulmonary metastasis showing bronchioloalveolar component; (B-E. hematoxylin and eosin stain; original magnification ×200).

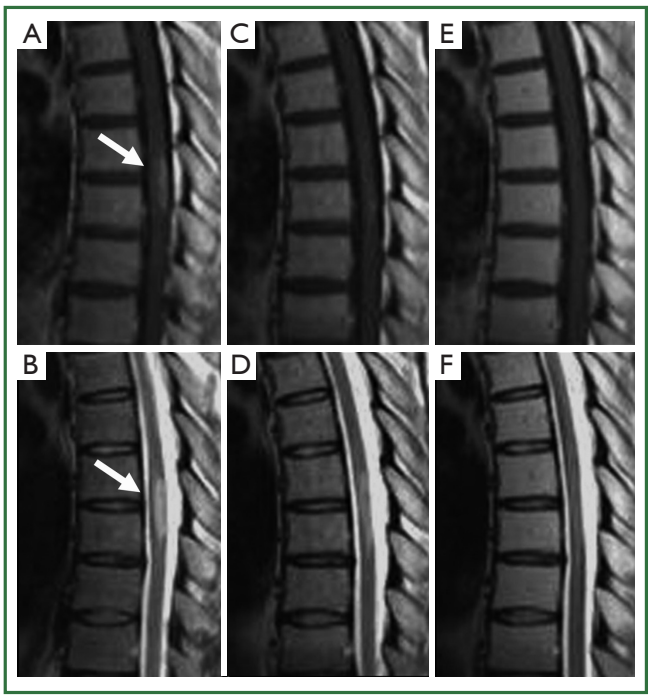

Figure 2. Changes of MRI findings. A. In November 2005, prior to treatment,gadolinium-enhanced T1-weighted image showing an enhanced lesion at Th7/8; B. T2-weighted image showing a larger high-intensity area with fusiform bulging; C. In January 2006, during the chemoradiotherapy with vinorelbin and cisplatin, gadolinium-enhanced T1-weighted image showing slight contrast effects remained. D. T2-weighted image showing mild high intensity area without fusiform bulging; E,F. In April 2006, 2 months after the initiation of gefitinib, MRI showed no abnormal findings on gadolinium-enhanced T1-weighted or T2-weighted images.

Although radiotherapy resulted in transient improvement, the symptoms worsened again during the 2nd cycle of chemotherapy (Figure 2C,D). In February 2006, gefitinib was administered. Symptoms improved after 2 weeks. The patient was discharged one month later, able to walk with slight numbness in both legs. Two months later, gadolinium-MRI showed no areas with abnormal contrast (Figure 2E,F). *EGFR* genetic analysis of the primary site was carried out retrospectively, but no activating mutations were found. The patient has remained in complete response for 7 years on gefitinib.

Discussion

MRI is sufficiently sensitive to detect intramedullary lesions, but the findings are not specific in that T2-weighted images are of high intensity for tumor and surrounding edema, and gadolinium-enhancement delineates central tumor. However, ISCM cannot be distinguished from primary spinal cord neoplasms or other non-neoplastic lesions such as demyelinating plaques, radiation myelitis, or paraneoplastic myelopathy on the basis of these MRI findings (4,6,7). The clinical course with rapid deterioration of neurological symptoms distinguishes ICSM from primary intramedullary tumors, which typically present with a slower progression of symptoms (2-4,6). In three-quarters of reported patients, the time from first onset of neurological symptoms to development of full neurological deficits is <1 month (2,3). Pain and weakness are more common early in the course, with sensory loss reported after. Bowel and bladder dysfunction most typically present later (6).

ISCMs constitute 1% to 3% of all intramedullary tumors. Lung cancer is the most frequent primary tumor (48%), followed by breast cancer (16%). At presentation, 26% of patients with ISCM have no identified primary tumor; most of these patients undergo surgery for decompression and diagnosis. In the remaining three-quarters, the primary is known. Most surgeons are reluctant to undertake aggressive resection because of the inherent risks of spinal cord operations and the advanced state of the systemic malignancy (4). Combination radiotherapy, steroids and chemotherapy is frequently applied, but efficacy depends on the sensitivity of the primary tumor. Surgical treatment might be considered for patients with radioresistant single metastases in the early stage of disease not yet with serious neurological deficits, and in the absence of multiple systemic metastases (4,8). However, survival benefit seems marginal. Median survival was 6 months in surgically-treated patients, 5 months in conservatively-treated patients, and one month for palliation. Functional improvement was observed in 58% of surgically treated patients, whereas 11% deteriorated. In patients treated with a conservative

regimen, 21% improved, 63% showed no change, and 17% deteriorated (4). ISCM has been frequently reported as well-circumscribed and amenable to gross total resection (1,9-11). On the other hand, infiltrative (12) or indistinct (6) margins, heavy bleeding (13,14), and disappointing postoperative course (14) has been reported, especially in ISCM from lung cancer. Thus, resectability might be determined by primary lesion histotype.

The present patient received chemoradiotherapy with steroids, followed by gefitinib, and has maintained a complete response(CR) for 7 years. Several uncertainties remain concerning diagnosis and treatment efficacy. The diagnosis of ISCM seems reliable, with the rapidly progressing neurological symptoms, which improved transiently after radiotherapy, then progressed again, but finally dramatically improved two weeks after starting gefitinib. Although later effects of radiation injury or edema cannot be excluded, the clinical course suggested that gefitinib was responsible for the favorable outcome. Despite lack of EGFR mutations in the primary lesion, they might have been present in the metastases (15). Five years after starting gefitinib, we considered withdrawal, but the patient wished continue and has now maintained a CR with excellent physical status for 7 years.

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