Abstract. Background: Patients with brain metastases of non-small cell lung cancer (NSCLC) have a poor prognosis, so chemotherapy and best-supportive care are typically pursued as initial treatments. Case Report: A 52-year-old man presented with symptoms of disorientation and disturbed consciousness as a result of multiple brain metastases. A histopathological examination revealed that the primary tumor was a large cell carcinoma located in the left upper lung. Whole brain irradiation (WBI) with a total dose of 50 Gy was immediately started. Since the brain tumors were successfully controlled, irradiation of the primary lung lesion with a total dose of 60 Gy was initiated 6 months after the WBI. Afterward, the patient was clinically free from lung cancer, but other cancers developed in the cecum and appendix and were surgically removed. He survived for more than 8 years after the WBI but eventually died of respiratory insufficiency caused by multiple lung metastases. The autopsy findings indicated that the lung lesions were metastatic adenocarcinomas from the appendiceal cancer, and the patient had remained disease-free from lung cancer. Conclusion: In view of the possibility of long-term survival in patients with stage IV NSCLC and brain metastasis, especially those with only intracranial metastases, careful consideration is be needed in the selection of treatment options.

Case Report

A 52-year-old man presented initially with disorientation and disturbed consciousness. He had been smoking 40 cigarettes per day for 32 years (Brinkman’s index: 1280) and had received a total gastrectomy for gastric cancer at the age of 42 years. Magnetic resonance imaging demonstrated gadolinium-enhanced multiple small nodules with extensive surrounding edema in the brain (Figure 1). He was diagnosed as having multiple brain metastases and WBI, using a conventional fractionation with a daily dose of 2 Gy, was immediately started. His consciousness level gradually recovered from the second week after the initiation of the WBI and he reached a normal level of consciousness after having received 30 Gy. After receiving a total dose of 50 Gy, the tumors completely disappeared (Figure 2). Meticulous examination by chest X-ray, chest and abdominal CT and bone scintigraphy revealed that the primary tumor was 2.1 cm in diameter and located in the left upper lobe of the lung. No extracranial metastatic tumors, including lymph node metastases, were...
observed (Figure 3). A biopsy specimen obtained by bronchoscopy confirmed that the histology of the tumor was large cell carcinoma (Figure 4). The clinical stage of the lesion was T1N0M1, according to the staging classification of the International Union Against Cancer (1994). In consideration of the patient’s quality of life, treatment for the primary lung tumor was postponed. He was discharged from hospital and was able to resume his normal work.

Six months after the initial treatment, the tumors in the brain were well controlled and irradiation of the primary lung tumor with a total dose of 60 Gy was initiated. The tumor showed a partial response at the end of the treatment and eventually disappeared. The patient had been clinically free from lung cancer for 4 years when an elevation in serum carcinoembryonic antigen (5.4 ng/ml) was noted. After a variety of examinations, an adenocarcinoma of the cecum (stage I) and an adenocarcinoma of the appendix (stage IIIa) were successively discovered. Both lesions were surgically removed (Figure 5) and the patient was once again able to return to work. Two years later, he presented with hemiparesis and dementia, possibly induced by the WBI. A few months later, the patient developed multiple lung metastases and pneumonia. He died of respiratory insufficiency caused by lung metastases more than 8 years after the initial WBI for multiple brain metastases.

An autopsy was performed and the findings confirmed the presence of multiple tumors in the lungs, para-aortic lymph nodes and paravertebral lesions; all of these lesions were diagnosed as metastatic adenocarcinomas from the appendiceal cancer (Figure 6). Regarding the brain findings, 2 microscopic lesions were found in the right and left frontal lobes; these lesions were suspected to be degenerated lesions of the metastatic tumors that had disappeared radiographically following radiation therapy. In fact, no viable tumor cells remained in either of the lesions. The lesion in the right frontal lobe was necrotic with calcification. Small vessels with thickly hyalinized walls, gliosis and foamy macrophages were observed around the necrotic focus. In the left frontal lesion, focally-proliferated hemosiderin-laden macrophages and foamy macrophages were found in the subcortical white matter and surrounding the vessels. Gliosis, including gemistocytic astrocytes, was observed around the lesions. The bilateral centrum semiovale appeared diffusely pale with myelin staining. In addition, hyalinized vessels and small patchy lesions were occasionally present in the areas of pallor. The small lesions showed marked loosening of the parenchyma and the proliferation of reactive astrocytes and macrophages with finely granulated cytoplasm. These lesion characteristics were compatible with radiation-induced leukoencephalopathy. Thus, no lung cancer cells were found in either the brain or the lungs and the autopsy confirmed that the patient was disease-free from lung cancer at the time of his death.

Discussion

Brain metastasis is frequently observed in patients with lung cancer, critically shortening the prognosis and lowering their quality of life. WBI has become recognized as a standard treatment for patients with multiple brain metastases, while
surgery and radio-surgery are indicated for single or a few brain metastases (1, 4, 5). According to the Radiation Therapy Oncology Group (RTOG) trials, the prognostic factors of patients with brain metastases can be identified by recursive partitioning analysis (RPA). Best survival was observed in patients less than 65 years of age and with a good performance status (Karnofsky performance status: equal or more than 70%), a controlled primary site and no extracranial metastasis (6). Thus, long-term survival may be achieved in a very limited number of patients in whom the primary lesion and brain metastases can be treated.

In the present patient, hemiparesis and dementia induced by the WBI appeared clinically 7 years after the initial treatment. Microscopically, no viable tumor cells were found in the 2 residual metastatic brain tumor lesions. Focal radiation necrosis typically occurs between 6 months and 2 years after radiotherapy, but our patient did not experience any focal symptoms affecting his job for 7 years, in spite of the possible presence of the lesions. The lesions were too small to be detected radiographically and the necroses were probably caused, not only by the normal tissue reactions to irradiation, but also by reactions associated with the tumors themselves. Radiation-induced leukoencephalopathy without necrosis is the most frequent complication in long-term survivors (7). An RTOG dose escalation trial for malignant glioma revealed that white matter changes were correlated with the radiation dose in long-term survivors (8). Although the follow-up period may not be sufficient to assess leukoencephalopathy in long-

Figure 2. CT axial image before whole brain irradiation (WBI) reveals metastatic tumors and extensive edema in the brain (a). The tumors had mostly disappeared, but the brain edema persisted at the end of irradiation (b). However, the edema had improved considerably 3 months after the WBI (c).

Figure 3. Chest radiograph showing a small nodule in left segmentum lobi superioris ventrale (S3).
term survivors, because long-term survival was defined as survival for at least 18 months, leukoencephalopathy was observed in only 8.3% of the patients who received 48 - 54.4 Gy of radiation in the RTOG trial. The incidence of leukoencephalopathy might be higher among patients who survive for more than 5 years, but few reports have analyzed leukoencephalopathy in 5-year survivors. In spite of the significant increase in leukoencephalopathy induced by WBI, the use of WBI in our patient was justified because it is currently the only treatment modality available for brain metastases of lung cancer.

The curative treatment options for primary lung tumors are mainly surgery, radiation therapy and combined chemoradiotherapy (CRT). In some retrospective reports, the 1- and 5-year survival rates of patients who underwent surgical treatments for both brain metastases and the primary lesions were 35 - 56% and 6.6 - 16%, respectively (9). Some reports have shown that CRT can achieve good results in NSCLC patients whose metastases are limited to the brain (2, 3). However, these results were obtained from a non-randomized trial in a small population.

No general management and treatment policy for lung cancer patients with brain metastases has yet been established. Some oncologists feel that these patients should
be treated with chemotherapy because their tumors can undergo latent extracranial hematogenous dissemination. However, it is difficult to control the primary site by chemotherapy alone. Some patients may also choose to receive best supportive care without curative treatment because of their poor general condition.

In the present case, the patient’s initial symptoms were serious and his general condition was poor because of the extensive brain edema caused by the brain metastases. Therefore, WBI was immediately initiated as an emergency procedure. After the metastases had been controlled, the patient received irradiation for the primary lung tumor; local control of this lesion was also achieved. An autopsy pathologically confirmed the disappearance of all lung cancer cells. We speculated that the patient’s lung cancer and multiple brain metastases were controllable because his initial symptoms were not due to the primary lung tumor, but to the brain metastases. The patient’s primary lung tumor was a stage T1N0 lesion at the time of its discovery and could be controlled. Furthermore, distant metastasis was limited to the brain. The prognosis of patients with brain metastasis is mainly governed by the characteristics of the primary tumor or the presence of extracranial metastatic lesions (6). In addition, our treatment schedule, which consisted of WBI followed by sequential irradiation of the primary lung tumor, might have been suitable for this particular patient because this treatment was successfully accomplished with no deterioration of his condition.

In this case, chemotherapy was not combined with radiotherapy. Systemic chemotherapy may be useful for some stage IV patients with extracranial metastases (10), but some chemotherapeutic agents may not be effective for intracranial metastatic lesions because of their inability to pass through the blood-brain barrier. Although hematogenous dissemination is an indication for systemic chemotherapy, the patient’s general condition and normal immune system function may worsen. Therefore, the use of chemotherapy for stage IV lung cancer patients without extracranial metastasis should be carefully considered because chemotherapy is not always effective or necessary for these patients.

In conclusion, definitive radiotherapy without chemotherapy to the primary site is indicated in a limited number of patients without extracranial metastasis and whose brain and primary tumors are both judged to be controllable. In view of the possibility of long-term survival in stage IV lung cancer with brain metastasis, customized treatment strategies are recommended.

References


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