GAMMA KNIFE RADIOSURGERY OF BRAIN METASTASIS FROM MALIGNANT PLEURAL MESOTHELIOMA – REPORT OF THREE CASES WITH AUTOPSY STUDY IN A CASE –

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ABSTRACT

The median survival time of malignant pleural mesothelioma (MPM) has been 9 months. Given the short survival, there have been only few cases in which brain metastases have been diagnosed and treated before death. Three cases of brain metastases treated by gamma knife radiosurgery (GKR) are reported. Case 1 showed a metastatic lesion in the right frontal lobe which was treated by GKR two years after diagnosis of MPM. The lesion markedly reduced and the symptoms were improved, but the patient died of progression of pleural tumor four months after GKR. A year and three months after the diagnosis, asymptomatic bifrontal lesions were treated with GKR. However, Case 2 died of abdominal mass a month after. Case 3 showed headache one and half year after the diagnosis. Three brain lesions were treated by GKR, which disappeared in 4 months. The patient died of new multiple brain metastases and periventricular dissemination seven months after. The autopsy revealed a MPM occupying the left pleural cavity. No neoplastic lesion was found in gamma knife-treated sites. The cause of death was the mass effect by new metastatic lesions. GKR was found effective also for the treatment of brain metastasis of MPM.

Key Words: brain metastasis, malignant pleural mesothelioma, gamma knife radiosurgery, asbestos exposure, autopsy study

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare and extremely malignant tumor. The time from diagnosis to death has been 4 to 12 (median 9) months.1,2) Almost 90% of male cases of MPM have reportedly been related to asbestos exposure.3) Although remote metastases are found in the liver, adrenal gland, kidney and lung, death is often due to the progression of the primary tumor. Brain metastasis is found in only 3% of cases.4) There have been many reports of brain
metastasis with verification by autopsy, in which only 7 cases were symptomatic before death, and surgical removal was done. The results of surgical removal with or without chemotherapy and/or radiation therapy have not been very effective. The life expectancy of MPM was limited by the shortage of new treatments for MPM. Recently, new chemotherapeutic drugs and boron neutron capture therapy (BNCT) have been effective for primary MPM. Therefore, treatment of brain metastasis of MPM will become more feasible. GKR was chosen for its effectiveness and less invasiveness in the treatment of brain metastases.

MATERIALS AND METHODS

We experienced two symptomatic and one asymptomatic brain metastases from MPM, which were treated by GKR and followed-up while the patients were alive as shown in Table 1. Three cases underwent GKR at Nagoya Radiosurgery Center using the Leksell Gamma Knife Model 4C (Elekta Instrument AB). Prescribed marginal dose was 20 Gy for those lesions. After the treatment, patients were evaluated by head MRI and neurological changes every two months.

RESULTS

A single large lesion decreased markedly at 3 months with improvement of symptoms after the treatment in Case 1 (Fig 1A) and three lesions disappeared in 4 months in Case 3 (Fig. 1B). No follow-up study was available in Case 2 because of early death of the patient. The response of metastatic lesions of MPM to GKR seemed similar to those of other malignant tumors, however two patients died by progression of primary lesions four and one month (Case 1,2) after GKR. Another died of new brain metastases and periventricular dissemination seven months after GKR (Case 3). It was also found that MRI and pathological study revealed complete disappearance of the metastatic lesions in Case 3 which were treated by GKR.

The time from diagnosis of MPM to death in 3 patients was 3 years, one year 4 months and 2 years 4 months, respectively, of which the mean survival time was 26.7 months.

PRESENTATION OF ILLUSTRATIVE CASE 3

A 71-year-old man had cough, sputum and left thoracic pain since middle of 2008. The patient had been working at a company with asbestos exposure for ten years since 1970. He showed weight loss of 5 kg in a month of summer and also had hemorrhagic pleural fluid accumulation in a month later, when a chest X-ray showed narrowing of left pleural cavity with pleural mass. Diagnosis of MPM was obtained by needle biopsy of pleura and cytology of the pleural fluid. Three courses of chemotherapy with carboplatin plus pemetrexed were undertaken in 2009, followed by 5 courses of pemetrexed alone and 4 courses of vinorelbine. The primary lesion seemed to be controlled. The patient complained of headache, in the early 2010, and brain MRI showed three round enhanced lesions 1 cm in diameter at the right and left frontal, and temporal lobe with perifocal edema (Fig. 1B, upper). Multiple liver lesions were also detected by abdominal CT. GKR was made for brain lesions with marginal dose of 20 Gy. Additional three courses of chemotherapy with carboplatin and gemcitabine were continued for the following 6 months. Three lesions had disappeared on MRI four months after the GKR (Fig. 1B, lower). No further follow-up by brain MRI was made and the patient showed gradual deterioration of sensorial level at 7 months after GKR. The final MRI revealed new, multiple brain metastases.
Table 1  Summary of Three Cases of Brain Metastases from MPM treated by Gamma Knife Radiosurgery

| Case #  | Age, Sex | State of Brain mets. | Symptoms of Brain mets. | Follow up – Months | Diagnosis of MPM: Diagnosis-Death, Cause of Death [Time] |
|---------|----------|----------------------|-------------------------|-------------------|-----------------------------------------------------|
|         |          | Locations            |                        | [Effects of GKR]  |                                                     |
|         |          | Number (Volume)      |                        |                   |                                                     |
| Case 1: 58 f |  Asbestos-exp. (-)   | (1) Rt-Front. single (4.0 ml) | Lt-hemiparesis | GK (1): - 3M [decreased] | 2005 – Diagnosis (1) |
|          |          | (2) Rt-Cbll, single (2.1 ml) | Headache | GK (2): - 1M [unknown] | 2008 – Diagnosis (2) |
|          |          |                       |                        |                   | 2008 – Death by Pleural T. [3Y] |
| Case 2: 65 m | Asbestos-exp. short (+) | (1) multiple mets. Lt-Front. (1.9 ml) | Asymptomatic | GK (1) - 1M [unknown] | 2007 – Diagnosis |
|          |          | (2) Lt-Front. (0.6 ml) |                        |                   | 2008 – Death by Abdom.T. [1Y4M] |
| Case 3: 71 m | Asbestos-exp. 10 years (+) | (1) multiple mets. Rt-Temp. (2.6 ml) | Headache | GK (1)-4M [disappeared] -7M multiple mets. & V. dissemination | 2008 – Diagnosis |
|          |          | (2) Rt-Front. (1.3 ml) |                        |                   | 2010 – Death by Brain mets. |
|          |          | (3) Lt-Front. (1.3 ml) |                        |                   | Autopsy [2Y4M] |

f=female, m=male, Y=year, M=month, T.=tumor, GKR=gamma knife radiosurgery, Rt=right, Lt=left, mets.=metastasis, exp.=exposure, GK=gamma knife V.=ventricular, Front.=frontal, Temp.=temporal, Cbll.=cerebellum, Abdom.=abdominal

Fig. 1  Follow-up MRI of Case 1 and Case 3 after Gamma Knife Radiosurgery:
(A) Rt-frontoparietal metastatic lesion (left MRIs) showed marked reduction 3 months after GKR (right MRI) in Case 1. (B) Three metastatic lesions (circles, upper MRIs) were disappeared at 4 months after GKR (lower MRIs) in Case 3.

with periventricular disseminations (Fig. 2A,B). The patient became comatous and died two weeks after the MRI study. Autopsy showed corresponding findings of MRIs (Fig. 2A, 2B) on coronal sections of the brain (Fig. 2C,D).
PATHOLOGICAL STUDIES OF AUTOPSY MATERIALS

MPM occupied the left intrapleural cavity and extended into the pleural diaphragma, mediastinum and the lung. Original pathological findings (Fig. 3A) changed to a more aggressive form by the metastasis to the brain (Fig. 3B). New metastases in the cerebrum and cerebellum with periventricular disseminated lesions were verified at autopsy (Fig. 2C,D). No tumor was found macro- and microscopically at the locations treated by GKR. Immunohistochemical studies of metastatic brain and lung lesions from autopsy revealed they were highly positive for calretinin,

Fig. 2 MRI and Autopsy Findings of Brain at Recurrence of Metastatic Lesions in Case 3.
Periventricular dissemination of the lateral ventricles and new multiple brain metastases are shown on T1 enhanced axial (A) and coronal MRI images (B). Corresponding lesions are shown in the coronal cerebral (C) and cerebellar (D) sections of autopsy brain.
focally positive for D2-40 and AE1/AE2, negative for CEA. A sign of tentorial herniation was found at the tectum of midbrain, which was thought to be the cause of death.

DISCUSSION

Asbestos exposure was initially found to be closely related to mesothelioma in 1960, and patients with asbestos-related mesothelioma have increased in numbers over the last few decades. A case control study had indicated that almost 90% of males with MPM have reported prior exposure to asbestos. One of our patients worked in a factory with asbestos exposure for 10 years and had been observed as a patient of pneumonopathy (Case 3). Case 2 had short-time asbestos exposure before diagnosis of MPM, and asbestos exposure was not confirmed in Case 1.

It has been recently found that the malignant change of asbestos exposure cells originated from excessive iron particles which accumulated in the cells. Prophylactic procedure to remove iron particles from the cells will be a preventive therapy for MPM.

MPM is classified into four pathological types; fibrous or sarcomatous, epithelial, undifferentiated, and mixed. Epithelial type is the most common and the sarcomatous type is the rarest but this type appears to be predominant in brain metastasis. It was confirmed that Case 3 had already been diagnosed as the epithelial type of MPM by biopsy, and a sarcomatous component was predominant in the brain metastasis at autopsy (Figure 3).

MPM typically spreads by local extension, and metastasis to the brain is rare. A review of 172 autopsy cases of MPM revealed that the most frequently involved organs were the liver (55.9%), adrenal glands (31.3%), kidney (30.1%), and the contralateral lung (26.8%). Brain metastases were observed in only 3% of cases. The majority of brain metastases of MPM were reported as autopsy cases, and only 9 patients had antemortem diagnosis, in which 7 cases undergone surgical removal. Regarding the treatment method, four of them were combined with radiotherapy and three were treated by surgery alone. The other two cases had undergone radiotherapy and radiosurgery alone. Two of four patients of combined treatment survived more than 36 months and the other two survived 6 and 8 months after surgery (mean of 21.5 months). Two patients treated by surgery alone survived only

Fig. 3 Pathological Findings of the Pleural Tumor and Metastatic Brain Tumor
HX-E stain show epithelial-type arrangement of pleural tumor (A), which is changed to sarcomatous arrangement in the metastatic brain tumor (B). ×200
The results of radiotherapy alone were also poor, but the present 3 cases survived a mean of 4.3 months after GKR (Table 1). MPM had a poor prognosis with a median survival time of 9 (4–12) months, but long-term survival can be expected by the application of new multimodal approaches such as new chemotherapy or boron neutron capture therapy for primary lesion. The mean survival of the present three patients was 26.7 months from diagnosis, two of which died of original tumor and one by brain metastases.

Stereotactic radiosurgery has developed as an indication for metastatic lesions. To our knowledge, this will be the first report of effectiveness of GKR for brain metastasis of MPM with combination of chemotherapy. Many opportunities for treating brain metastasis with MPM will emerge in the future not only by stereotactic radiosurgery but also by stereotactic radiotherapy.

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CONFLICTS OF INTEREST DISCLOSURE

The authors have no personal, financial or institutional interest in any of the drugs, materials or devices in this article.

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