Two Malignant Mesothelioma Cases with Brain Metastasis

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To the Editor,

A 32-year-old male patient presented to our clinic in February 2014 with complaints of chest pain and dyspnea, which lasted for the last six months. In the x-ray examination,the right sinus was closed and there was the pleural effusion (Figure 1). The patient was performed recurrent thoracentesis within six months and the pleural biopsy was reported as malignant mesothelioma. The patient was evaluated to be suitable for operation; therefore, a 30% right pleurectomy and decortication were performed on March 2014 and the patient was administered hyperthermic perfusion chemotherapy with cisplatin intraoperatively.The postoperative pathology examination was reported to be consistent with epithelioid malignant mesothelioma. The immunohistochemical staining revealed CK 5/6 in neoplastic cells; EMA positivity; calretinin was weak-positive and there were negative reactions for CEA, BerEp4, and desmin. In April 2014, adjuvant cisplatin+pemetrexed treatment was initiated. After six courses, the disease progressed and a gemcitabine regimen was initiated in May 2014. The patient developed headache, nausea and vomiting while stable with six courses of gemcitabine treatment. The cranial MR revealed lesions in the left cerebral hemisphere, the largest of which was in the insular cortex with a diameter of approximately 1 cm and hypointense in the T1A sequence and hyperintense in the T2A sequence with contrast enhancement. It had an intense edema effect and was evaluated as metastasis (Figure 1). In the thorax abdominopelvic computed tomography(CT) in addition to mass lesions filling the right hemithorax in the CT, metastatic nodules of 1 cm in the left lung and the liver. Dexamethasone treatment for cranial metastases and palliative radiotherapy (3 Gy x10 fraction) were initiated. The disease progressed and after palliative radiotherapy, cisplatin+etoposide treatment was initiated in May 2015. A stable response was obtained after the third course and it was planned that chemotherapy would be completed at the sixth course. Palliative chemotherapy of the patient is ongoing.

A 43-year-old female patient presented in October 2007 with complaints of presence and progression of effort dyspnea for two months, coughing, sputum formation and pain on the left side of the chest. In the x-ray examination, a mass extending from the left hilar region to upper zone, and blunting of the left sinus were observed (Figure 2). A solid lesion with a diameter of approximately 11.5x10 cm, which was not markedly contrast enhancing, heterogeneous, and starting from left suprahilar level and extending to superior medial, also covering partially aorta, upper lobe bronchus, artery and vein was diagnosed in thoracic CT. There was also pleural fluid and non-calcific pleural plaques in the CT scan. In the positron emission tomography/computed tomography (PET/CT), a mass lesion measuring 11x10 cm in diameter (suv max: 6.1), which had irregular borders, heterogeneous FDG uptake, and located centrally in the

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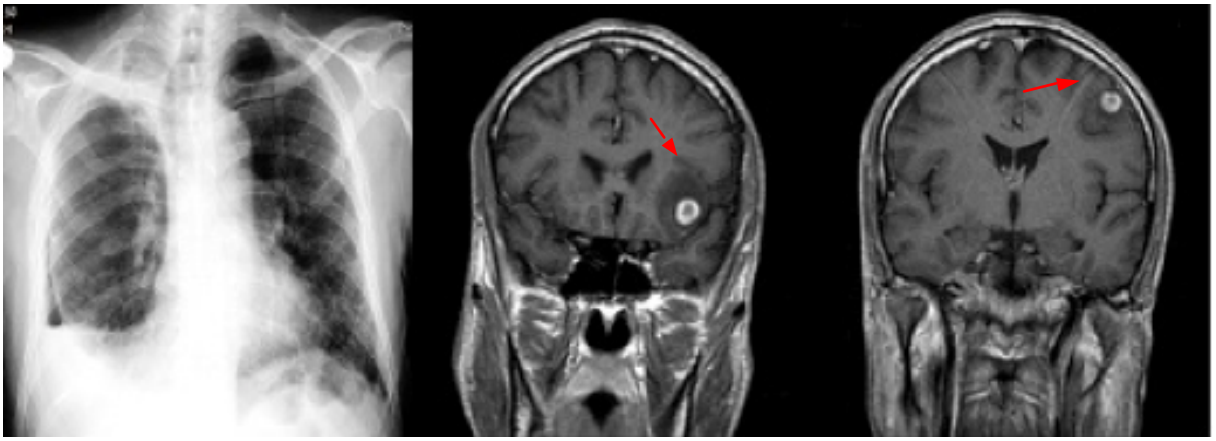

Figure 1. Chest x-ray and cranial MR imaging of the first patient

anterior segment of the upper lobe of the left lung, in close proximity to upper mediastinal structures while pushing them and diffuse pleural effusion without FDG enhancement in the left hemithorax were diagnosed. Pleural biopsy was reported as biphasic malignant mesothelioma. Immune histochemical staining results were positive for CK 7 and calretinin, and negative for TTF-1 and CK 20.

The patient was accepted as surgically inoperable and palliative cisplatin+pemetrexed treatment was initiated in November 2007. A partial response was observed in the evaluation that was performed after three courses.The patient became symptomatic after 18 months follow-up with stable disease, progression was diagnosed in imaging examinations and therefore, six courses of cisplatin+pemetrexed were restarted in June 2009. After six courses, the patient was followed-up with stable disease for 12 months. The disease progressed one year later and therefore six courses of carboplatin+gemcitabine was initiated in June 2010. Stable disease was diagnosed after three courses and disease progression was diagnosed after six courses. In the imaging examinations, in addition to the mass increase in the upper lobe in the left lung, there were newly formed parenchymal nodular lesions measuring 2 cm in diameter. The patient received two sessions of dendritic cell vaccine therapy in Koln in April 2011. Progression was observed after six months and single agent pemetrexed was administered to the patient in January 2012. After six courses, the patient was followed-up with stable disease for approximately two years. After clinical and radiological progression, the patient received cisplatin docetaxel. During chemotherapy, patient applied to our emergency unit with convulsions on February 26, 2015. The cranial MR revealed nodular lesions consistent with metastasis, which showed intense homogenous contrast enhancement, iso-hypointense in T1 and T2 weighted sequences and approximately 10 mm in diameter located at gyrus in right temporoparietal lobe; 9.5 mm in diameter in white matter of parietal lobe in the left parasagittal area at the centrum ovale plane, 6.5 mm in diameter located at gyrus in posterior parieto-occipital lobe at the ventricular plane 5 mm and 3 mm in diameters (Figure 2).Dexamethasone treatment and palliative RT(4 Gyx5 fraction) were initiated. The general state of the patient did not improve after the treatment, and she died on March 13, 2015.

Malignant mesothelioma is one of the rare tumors originating from serosal surfaces, is related to asbestos exposure, and has an aggressive progression.Malignant mesothelioma has three subtypes: epithelioid, sarcomatoid, and biphasic. It is known that the sarcomatoid type has a poorer prognosis.[1] Mesothelioma progresses through local invasion and has limited metastasis characteristics. Many patients apply with unresectable disease at the time of diagnosis and its prognosis is poor. Despite multimodal treatments, the mean survival rate is 12-36 months in local diseases and the mean survival is 8-14 months in the advanced stage disease.[2]

Generally, brain metastasis develops in 9-17% of cancer patients.[3] Brain metastasis incidence and

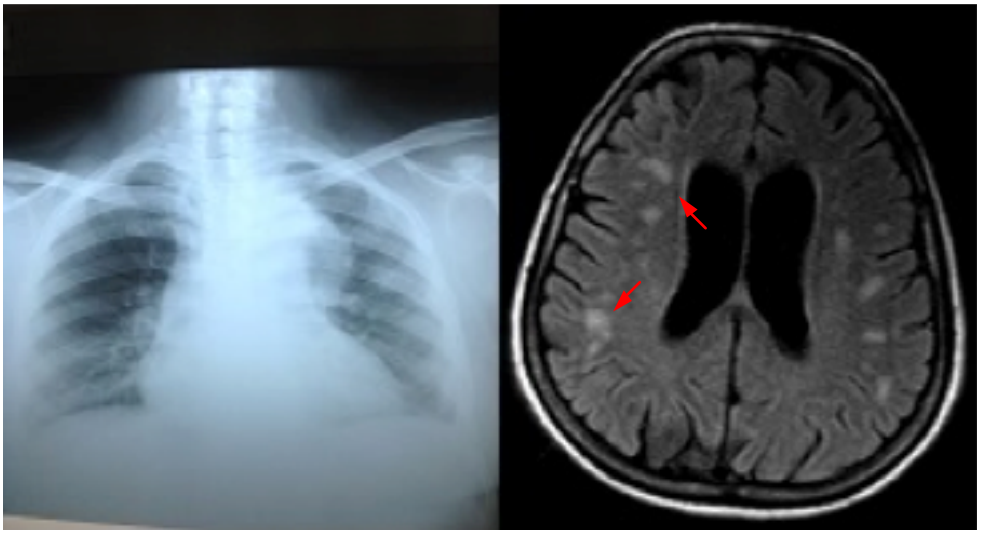

Figure 2. Chest x-ray and cranial MR imaging of the second patient

metastasis patterns are not clearly known in malignant mesothelioma, which generally shows local invasion. However, autopsy studies determined that distant metastasis rates of mesothelioma are not actually low. A study evaluating an autopsy series determined that the rate of brain metastasis was 3%.[4] Brain metastasis is a poor prognostic sign in cancer patients. When brain metastases are compared to other parts of body, it is related to systemic chemotherapy resistance It is believed that this resistance is due to passage through the blood-brain barrier . The mean survival rates are one to two months and six to eight months in untreated patients with brain metastasis with aggressive treatment.[3]

Although malignant mesothelioma spreads typically by local invasion, distant metastasis may also be observed. However, it is believed that brain metastasis is very rare. Studies evaluating autopsy series determined that distant organ metastasis of mesotheliomas are more common than expected.[5] The incidence of brain metastasis in malignant mesothelioma is not definitely known The majority of reported cases were defined after postmortem evaluations. Falconieri et al. examined the autopsies of 171 malignant mesothelioma patients. They reported that 54% of patients had distant metastasis and the most frequently observed areas were determined as liver,adrenal glands, and kıdneys (56%, 31%, and 30%, respectively). Cerebral metastasis was determined at a rate of 3%.[4] In another study investigating the autopsy findings in mesothelioma, it was determined that distant metastasis occurred at a rate of 50%, and brain metastasis was 5-10%.[6]

In the review of Miller et al which included seven studies with 655 patients, the brain metastasis rate was reported as 2.7% and it was shown that the sarcomatoid subtype was higher among patients with brain metastasis. It was also determined that 11% of brain metastasis were histologically different from primary tumors in patients with brain metastasis and they showed histological differentiation to a more aggressive subtype.[7] The pathologies of one of our patients was epithelioid and the other was biphasic. As brain metastases were not appropriate for surgery, and thus we did not have the opportunity to evaluate the pathologies of brain metastases and we could not evaluate our patients for the aggressive subtype of transformation.

The retrospective study performed by Yamagishi et al which included 150 patients with malignant mesothelioma was the first and only study investigating risk factors related to brain metastases and evaluating survival outcomes in addition to the incidence of brain metastases. Brain metastases were determined in 5.3% of 150 patients and it was reported that an age younger than 65 years and stage IV disease were related to brain metastasis but the histological subtype was not a risk factor for brain metastasis. It was determined that the prognosis of

patients with brain metastasis was worse than those without the metastasis (OS: 6.5 vs. 11.0 months).[8] Our two cases belonged to the brain metastasis risk group because they were young and had metastatic diseases.

Brain metastases develop in approximately two to three years in cancer patients.[9] In mesothelioma patients who locally invasive progression and mean survival duration is short, brain metastasis incidence increased in recent years. Improvements in systemic treatments of mesothelioma, which is relatively resistant to chemotherapy and radiotherapy, so increased survival durations and improvements in imaging methods are factors that contribute to an increased incidence of distant metastasis in course of disease.In our cases, brain metastases developed in the seventh year in one patient, and in the second year in the other. Survival outcomes were worse after brain metastasis.

In conclusion, recognition of rare clinical features of mesothelioma is important in directing the treatment of the disease.

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