Brain and Skull Metastases of Hepatic or Pancreatic Cancer
—Report of Six Cases—

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Abstract

Brain and skull metastases from primary hepatic or pancreatic cancer are very rare. The authors describe six cases of metastatic tumors. These are skull (three cases) and brain (one) metastasis of hepatic cancer and brain metastasis (two) of pancreatic cancer. In three hepatic cancer patients, the metastatic lesions were diagnosed before the diagnosis of primary cancer. In these patients, plain skull x-ray showed osteolytic lesions and vascular enlargement. A postcontrast computed tomographic (CT) scan showed an enhanced high-density epidural mass. Angiograms showed a tumor stain fed by abnormal vessels from the external carotid artery. In one patient with a metastatic brain tumor from hepatic cancer, a CT scan showed a high-density mass with hematoma. In one of the brain metastases from pancreatic cancer, a CT scan revealed a cystic, ring-like enhanced lesion in the thalamus. In the other case, a CT scan showed an isodensity mass in the vermis and hydrocephalus. Metastatic tumors from primary hepatic cancer were soft and hemorrhagic, but they were clearly demarcated from the surrounding tissue. In the case of thalamic metastasis, the cyst content was aspirated and an anticancer agent was administered into the cystic cavity. In the other cases, the tumors were totally removed. The outcome was very poor in all cases.

Key words: brain neoplasms, metastasis, hepatic cancer, pancreatic cancer, skull tumor

Introduction

The incidence of metastatic brain tumors is increasing because advances in the detection and treatment of primary cancer have led to longer survival periods. According to the Brain Tumor Registry in Japan, the proportion of metastatic brain tumors among whole brain tumors increased from 10.8% in 1969 to 12.1% in 1976 and to 13.9% in 1981. More than half of the primary cancers were lung and breast cancers; metastatic brain tumors from cancer of the digestive system are relatively rare. The prognosis of patients with hepatic and pancreatic cancer is very poor. These cancers rarely metastasize to the central nervous system (CNS). However, advances in the treatment of hepatic and pancreatic cancers have also led to an increase in the incidence of metastases of these cancers to CNS.

We present six cases of metastatic tumors; three skull and one brain metastases from hepatic cancer and two brain metastases from primary pancreatic cancer.

Case Reports

I. Brain metastasis from hepatic cancer

Case 1: On February 24, 1982, a 60-year-old male experienced a sudden onset of right hemiparesis and aphasia. Two years prior to admission, he had undergone hepatic cancer surgery.

On admission, general examination showed no abnormalities. Laboratory examination showed the levels of serum α-fetoprotein (AFP) and carcino-embryonic antigen (CEA) were 4 and 5.9 ng/ml (normal, under 5 ng/ml), respectively. Neurological examination revealed sensory aphasia and right hemiparesis. A plain skull x-ray was negative. A precontrast CT scan demonstrated a round high-density mass in the subcortex of the left posterior temporal lobe (Fig. 1). Angiography showed a space-occupying
II. Skull metastasis from hepatic cancer

Case 2: In December, 1982, a 73-year-old male noticed an indolent thumb-sized mass in the right occipital region of the skull. The mass slowly grew. On admission, general examination showed no abnormalities. The tumor was $7 \times 5$ cm in size and pulsating. Compression of the occipital artery decreased the pulsation. A plain skull x-ray revealed a bone defect around the right lamboid suture. A precontrast CT scan demonstrated a convex high-density mass in the epidural space with significant enhancement (Fig. 3). Right external carotid angiography showed a tumor stain fed by the right occipital and retroauricular arteries and obstruction of the right transverse sinus (Fig. 4). Laboratory examination revealed mild liver dysfunction and an increased serum CEA level (15 ng/ml). The serum AFP level was within the normal range. At surgery, a soft, hemorrhagic, well-demarcated tumor was totally removed. The tumor had not invaded the dura or the subcutaneous tissue but the bone around the tumor showed destruction and hemorrhage. The histological diagnosis was hepatocellular carcinoma.

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Postoperatively, a mass in the left lobe of the liver was identified by echogram and he was transferred to the general surgical department. He died 6 months later.

**Case 3:** In August, 1986, a 61-year-old male noted an occipital mass and was admitted on November 17.

On admission, general examination revealed palmar erythema and vascular spider, and laboratory examination showed mild liver dysfunction. The serum AFP level was slightly high (24 ng/ml) and serum CEA was within normal limits. Neurological examination showed no abnormalities. A plain skull x-ray revealed a round bone defect at the inion and dilatation of the groove of the blood vessel. CT scans showed a convex high-density mass with significant contrast enhancement. An external carotid angiogram indicated dilatation of the branches of the middle meningeal artery and the occipital artery. An echogram and CT scans of the abdomen demonstrated a mass in the left lobe of the liver and cirrhosis. At surgery, the skull tumor was soft and red-brown in color. It was easily suctioned and totally removed; there was no dural attachment. The histological diagnosis was hepatocellular carcinoma. Although he underwent therapy for the primary hepatic lesion, he died in January, 1988.

**Case 4:** A 59-year-old male visited the department of internal medicine in October, 1986, complaining of headache. A liver echogram showed a mass and a plain skull x-ray showed a bone defect. He was admitted to our department on March 19, 1987. Five years prior to admission, he suffered from serum hepatitis.

On admission, general examination revealed palmar erythema, vascular spider, hepatomegaly, and a subcutaneous mass at the midline of the forehead. Neurological examination indicated no abnormalities. A skull x-ray showed an irregular bone defect measuring 4 × 5 cm at the midline of the frontal bone and a chest x-ray showed a bone defect of the right 8th rib. A CT scan revealed a convex high-density mass with significant enhancement in the epidural space extending into the subcutaneous space. At surgery, the tumor adhered to and invaded the dura and was hemorrhagic. The tumor portion attached to the superior sagittal sinus wall was not removed. Histological diagnosis was mixed-type cholangiocellular carcinoma and hepatocellular carcinoma. He underwent treatment for the primary lesion; he died 1 month after discharge due to liver dysfunction, however.

**III. Brain metastasis from pancreatic cancer**

**Case 5:** In March of 1980, a 56-year-old male developed right hemiparesis, and was admitted on May 5. One year prior to admission, he had undergone surgery for cancer of the pancreas head.

On admission, general examination revealed no abnormalities. Neurological examination showed a mild disturbance of consciousness, anisocoria, right hemiparesis and hemihypesthesia. Skull and chest x-rays were unremarkable. A precontrast CT scan revealed a low-density mass in the left thalamus (Fig. 5) which had ring-like enhancement by contrast medium. The serum AFP level was within the normal range. On May 16, a biopsy was performed and an Ommaya reservoir was emplaced. The cyst content was yellow, turbid mucus and only cell debris were detected. Neocarzinostatin (total 150 μg) was injected into the tumor cavity and local radiation therapy (total 50 Gy) given. A lymph node swelling in the left supraclavicular region was noted at this time. The lymph node tumor was removed and histologically diagnosed as adenocarcinoma. The disturbance of consciousness gradually improved and the size of left thalamic mass decreased. He underwent rehabilitation for right hemiparesis. He died in February, 1981, due to pneumonia.

**Case 6:** In May, 1986, a 58-year-old male complained of lower abdominal pain. At this time, pancreatic cancer was identified. However, he had received conservative therapy because of liver metastasis. Dizziness and headache developed and he was hospitalized in October, 1986. On admission, a postcontrast CT scan revealed an irregularly enhanced isodensity mass in the cerebellar vermis (Fig. 6). On October 17, the tumor was totally removed. It was red in color and relatively firm and...
clearly demarcated from the surrounding tissue. The histological diagnosis was adenocarcinoma of signet-ring cell type (Fig. 7). The fourth ventricle was opened and the ventricular wall was intact. Postoperative course was uneventful. However, cancer cells were detected in the cerebrospinal fluid. A follow-up CT scan showed meningeal carcinomatosis. He died due to gastrointestinal tract bleeding on October 30, 1986.

Table 1 shows the clinical summary of these six cases.

### Discussion

#### I. Incidence

The incidence of brain metastases from the digestive system is lower (6.8%–7.8%) than from lung and breast cancers. Takakura reported that 26 (57%) of 46 cases were metastases from the primary stomach cancer. Metastases from hepatic or pancreatic cancer are rare. According to the Brain Tumor Registry in Japan, of 3262 metastatic brain tumors, 40 (1.2%) were from hepatic cancer and none from pancreatic cancer.

Takakura reported that the primary cancer was hepatic or pancreatic cancer in only 7% of brain metastases from cancer of the digestive system. In the series of Berlit and Gänshirt, of 353 metastatic brain tumors, 2 (0.6%) were derived from hepatic cancer and one (0.3%) from pancreatic cancer. In only 2 (0.5%) of 400 patients who died of hepatic cancer did an autopsy reveal brain metastases. According to Tokoro, the incidence of brain metastases from hepatic or pancreatic cancer was about 1–2%. The low incidence of brain metastasis may be a characteristic of hepatic and pancreatic cancer.
i.e., non-affinity for the brain or poor prognosis of the primary cancer. Although brain metastases from colon cancer are rare, 11 colon cancer is thought to metastasize easily to the brain. 19

The metastatic route to the brain or skull is generally hematogenous through the lung, heart, and main circulation. 7 In a series of hepatic cancers, 7 tumor emboli were seen in the vena portae or hepatic vein. In a pancreatic cancer series 12 the main route was lymphatic in the curable stage and hematogenous in the severe progressive stage.

Watanabe et al. 23 reported that among 52 metastatic tumors, three (6%) were metastatic skull tumors. We have encountered nine metastatic skull tumors, except for melanoma cases and malignant tumors directly invading the skull (unpublished). Among these nine skull tumors, five were in the skull base and four in the skull vault. Of the latter, one had metastasized from thyroid cancer and three metastasized from hepatic cancers. Although skull metastases from hepatic cancer are rare, 1,2,5,8,14 hepatic cancer should be kept in mind as the primary lesion in cases of metastatic skull tumor.

The incidence of hepatic and pancreatic cancers is increasing. With improvements in the treatment of these primary cancers, the incidence of metastases from these cancers to the brain and skull may further increase.

II. Clinical observations

In all three cases of skull metastases from hepatic cancer, the diagnosis of metastatic lesion preceded that of primary lesion. Nakao et al. 14 also reported that in three cases of skull metastases from hepatic cancer, the metastatic lesions were detected before the primary lesions. This is probably due to the fact that early diagnosis of hepatic cancer is difficult while skull lesions can be detected easily. On the other hand, in our series, in two cases with pancreatic cancer the diagnosis of primary lesion preceded that of the metastatic lesion by 5 and 15 months, respectively. They are very short compared to the 3 years on average we reported for five cases of colon cancers. 11

Skull metastases from hepatic cancer may present as subcutaneous masses. Our patient with brain metastasis from hepatic cancer developed intratumoral hemorrhage. Ohno et al. 16 reported a similar case. Although reports on the intratumoral hemorrhage of metastatic lesions from hepatic cancer are scarce, angiograms of hepatic cancer show hypervascularity and these cancers tend to hemorrhage.

All of our hepatic cancer patients were male as were all three patients reported in another series. 14

The incidence of hepatic cancer is 4.8 times higher in males than in females. 20 The incidence of pancreatic cancer is 1.6 times higher in males than in females. 7

Tanaka et al. 20 reported that the measurement of serum AFP level was valuable for the diagnosis of hepatic cancer in 68.9%. However, we found it to be significantly increased in only one of the three cases so examined in our series.

III. Neuroradiological examination

In the patients with skull metastases from hepatic cancer, skull x-rays showed irregular defects and dilatation of the groove of the feeding arteries extending to the tumor. CT scans showed bone defects and a convex high-density mass with significant homogeneous enhancement. An external carotid angiogram showed feeding arteries and a tumor stain. In the patient with brain metastases from hepatic cancer, a CT scan showed a high-density mass due to hemorrhage. There are few reports of CT findings in patients with brain metastases from hepatic cancer. Ohno et al. 16 reported one case in which a CT scan showed a high-density mass due to hemorrhage. Because hepatic cancers are characteristically rich in vessels, precontrast CT scans tend to show high density. In cases with brain metastases from pancreatic cancer, CT scans showed findings similar to those of brain metastases from cancers of other digestive organs. 24 In one of our two cases, a CT scan showed a cyst with ring-enhancement; in the other case, it showed an isodense mass with homogeneous enhancement.

IV. Treatment and prognosis

Treatment of hepatic and pancreatic cancers with brain or skull metastasis is very difficult. Surgery is the best treatment in patients with hepatic cancer. Radiation therapy is not effective against hepatic cancer due to the low radiosensitivity of hepatic cancer cells. 5,15 Because most hepatic cancer patients have accompanying liver cirrhosis, the systemic administration of anticancer agents causes side effects. Therefore, local intra-arterial administration of anticancer agents has been recommended. 17 Although pancreatic cancer is also resistant to radiation therapy, intraoperative irradiation against the primary lesion has been recommended. 12 The recommended combined chemotherapy for pancreatic cancer includes 5-fluorouracil. 13

If radiation therapy is not effective against the primary lesion, the metastatic lesion must be treated. When contemplating surgical treatment for metastatic lesions, the number and location of the metastatic lesion(s), the patient's general condition,
the status of the primary lesion, and the possible presence of metastasis to other organs must be considered. Surgical treatment may prolong life and mitigate suffering. Especially in cases of skull metastasis, excepting metastasis to the skull base and multiple metastases, the surgical risk is lower than in patients with brain metastasis. Removal of the skull tumor can reduce suffering. But in the case of brain metastasis, any decision to intervene surgically must be made with great care. After consulting specialists about the condition of the primary lesion and the possible presence of metastasis to other organs, we discussed the effects of anesthesia and the patients' prognosis. In Case 6, a patient with cerebellar metastasis in the end stage of pancreatic cancer, operation was probably contraindicated, however, surgery was performed at the request of the family. This patient died 2 weeks later.

In two of the three skull metastases from hepatic cancer, the tumor was totally removed. The tumors were soft and easily separated from the dura. In the case with brain metastasis from hepatic cancer, the tumor was totally removed. The characteristics of the brain tumor were similar to those of the skull tumor. All patients died an average of 7.5 months after the diagnosis of metastatic lesions. In our patients with brain metastasis from pancreatic cancer, we aspirated the cyst content and administered anticancer agent into the cyst cavity in one case and totally removed the tumor in the other case. However, the patients died an average of 4.7 months after the diagnosis of the metastatic lesions due to complications.

Because of the possibility that cancer cells invading the surrounding tissue still remain after surgery, we need auxiliary treatments to prolong survival. Radiation is not effective and chemotherapy of limited applicability due to liver cirrhosis. However, the administration into the carotid artery and the tumor cavity of anticancer agents against metastatic lesions are expected to have similar effects to intraarterial administration into the primary lesion. On the other hand, because the prognosis for primary pancreatic cancer is very poor, surgery for brain metastasis is rarely useful. But if the primary lesion is well controlled, local therapy for the metastatic lesion may be useful in prolonging life and alleviating suffering.

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