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【 CASE REPORT 】

Treatment Outcome of Nab-paclitaxel Plus Gemcitabine for Leptomeningeal Carcinomatosis from Pancreatic Ductal Adenocarcinoma: An Autopsy Case Report

Kunio Iwatsuka[1], Daiichiro Kikuta[1], Hitoshi Shibuya[1], Masahiro Ogawa[1], Takuji Gotoda[1], Mitsuhiko Moriyama[1], Hiroshi Nakagawara[2], Akihiro Hemmi[3] and Kenji Yamao[4]

Abstract:
A 57-year-old woman with a sudden-onset seizure was hospitalized. Brain magnetic resonance imaging findings led to a suspicion of leptomeningeal carcinomatosis (LMC) without a brain parenchymal tumor, and abdominal computed tomography showed a tumor in the pancreatic tail. Endoscopic ultrasonography-guided fine needle aspiration of the pancreatic mass revealed adenocarcinoma. Therefore, LMC from pancreatic ductal adenocarcinoma was strongly suspected. She received three courses of nab-paclitaxel plus gemcitabine and whole-brain radiation. Shortly thereafter, she developed a severe consciousness impediment and died. A pathological autopsy showed adenocarcinoma in a wide area of the leptomeninges.

Key words: leptomeningeal carcinomatosis, pancreatic ductal adenocarcinoma, chemotherapy, radiation therapy

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Introductiofn

Metastatic leptomeningeal carcinomatosis (LMC) is defined as infiltration of the leptomeninges by malignant cells and it is a fatal complication of cancer (1-5). LMC is estimated to occur in from 3% to 8% of patients with solid cancers (6) and it is a devastating complication of such cancers; the median survival time is less than 2 months without treatment (7). In patients with pancreatic ductal adenocarcinoma (PDAC), metastasis to the central nervous system (CNS) is generally rare (occurring in approximately 0.3% of all cases) (8). In particular, the development of LMC metastasis is quite rare: only 17 cases of LMC from PDAC have been reported to date (9-25). LMC is a serious complication of PDAC with an extremely poor prognosis and limited treatment options. Few articles to date have described the treatment approach for LMC from PDAC (11, 13-15, 18, 19, 23, 25). In this report, we present an autopsy case of LMC from PDAC in a patient who was treated with nab-paclitaxel plus gemcitabine (nab-PTX+GEM).

Case Report

A 57-year-old woman without any notable medical history was transferred to our hospital by ambulance because of a sudden-onset seizure. The seizure was stopped by the intravenous injection of diazepam. However, her severe consciousness impediment did not improve. Symptoms of meningeal irritation (stiff neck, Brudzinski's sign, and Kernig's sign) were not present. Magnetic resonance imaging (MRI) of the brain revealed edematous cerebral parenchyma of the right frontal lobe (Fig. 1A) and leptomeningeal enhancement around the right to left cerebral folia (Fig. 1B). Although leptomeningeal metastasis was suspected, a brain parenchymal tumorous lesion was noticeably absent. Abdominal computed tomography (CT) showed a tumor in the tail of the pancreas, and the tumor was invading the splenic

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine Graduate School of Medicine, Japan, [2]Division of Gastroenterology, Yokohama Chuo Hospital, Japan, [3]Division of Pathology, Nihon University School of Medicine Graduate School of Medicine, Japan and [4]Department of Gastroenterology, Narita Memorial Hospital, Japan
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Correspondence to Dr. Kunio Iwatsuka, knwtsk29@gmail.com

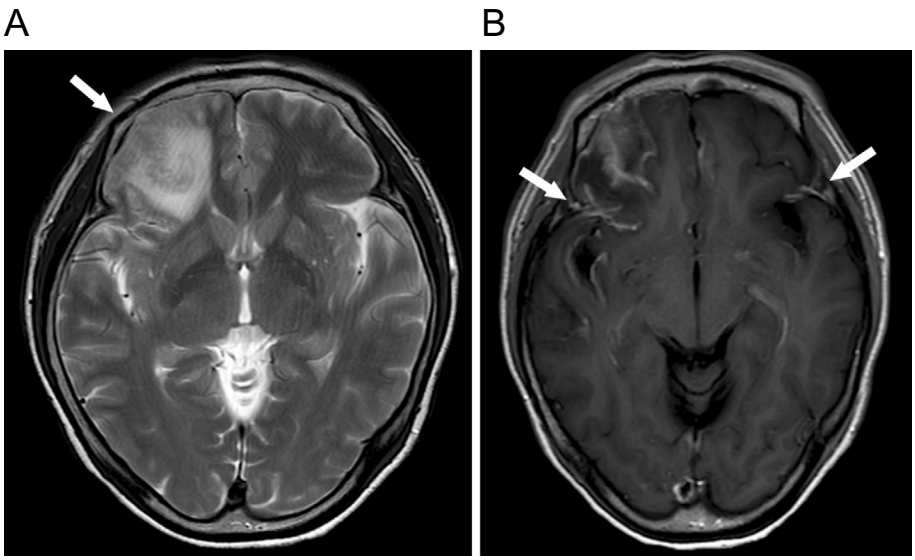

Figure 1. **Brain magnetic resonance imaging (MRI). (A) T2-weighted brain MRI revealed edematous cerebral parenchyma of the right frontal lobe (arrow). Parenchymal involvement was noticeably absent. (B) Contrast-enhanced brain MRI showed partial enhancement around the right to left cerebral leptomeninges (arrow).**

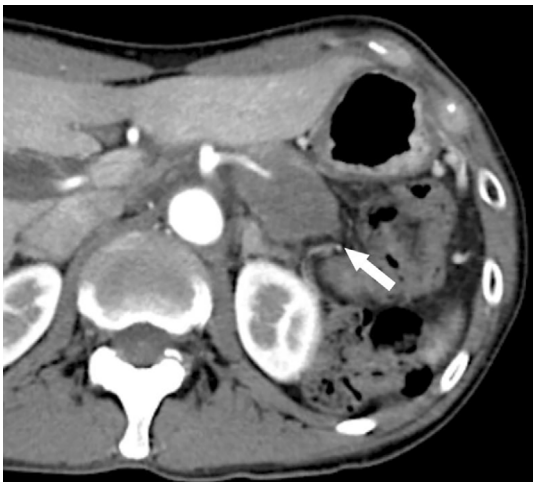

Figure 2. **Contrast-enhanced computed tomography. Contrast-enhanced abdominal computed tomography showed a tumor in the tail of the pancreas. The tumor invaded the splenic artery and vein (arrow). Distal metastasis was not detected.**

artery and vein (Fig. 2). The tumor was hypovascular and poorly enhanced compared with the surrounding pancreatic parenchyma in the early phase of dynamic CT and it became gradually enhanced on delayed images. Distal metastasis was not detected on chest or abdominal CT. Laboratory blood tests revealed high levels of tumor markers: carbohydrate antigen 19-9, 518 U/mL (reference range, <30 U/mL); DUPAN-2, 2,500 U/mL (reference range, <150 U/mL); and SPan-1, 1,800 U/mL (reference range, <30 U/mL). The carcinoembryonic antigen level was within the reference range at 2.0 ng/mL (reference range, <5 ng/mL).

Based on these findings, LMC from PDAC was suspected. Because the cause of the consciousness impediment was considered to be intracranial hypertension associated with LMC, an osmotic diuretic (600 mg of glycerol per day) and steroids (3.3 mg of dexamethasone per day) were administered as neurogenic symptomatic therapy. Her consciousness gradually improved: her Japan Coma Scale score on the first, second, and fourth days after admission was III-200, II-10, and I-1, respectively. Beside the consciousness impairment, headache, nausea, and limb numbness were seen. These neurogenic symptoms also suggested that LMC had caused intracranial hypertension.

On the 12th day after admission, endoscopic ultrasonography-guided fine needle aspiration of the pancreatic mass lesion was performed, and ductal adenocarcinoma was identified. As a result, the patient was clinically diagnosed with PDAC (cT3N1M1 Stage IV). In general, LMC is definitively diagnosed by cerebrospinal fluid (CSF) cytology via a lumbar puncture. However, multiple lumbar punctures are sometimes needed because of the low sensitivity of CSF cytology for malignant cells (26). The patient refused lumbar puncture because of the period of time required to achieve a definitive diagnosis and the possible complications of lumbar puncture. Therefore, we prioritized treatment for PDAC, and systemic chemotherapy was begun 19 days after admission.

We chose the combination of nab-PTX+GEM, which was the first-line regimen for unresectable PDAC at that time in Japan. The regimen comprised nab-PTX (125 mg/m^2) followed by GEM (1,000 mg/m^2) administered on days 1, 8, and 15 every 4 weeks (one cycle). Shortly after chemotherapy administration, the patient developed an exacerbation of her headache and a left hearing impairment associated with LMC. Thus, a total of 20 Gy of whole-brain radiation therapy (WBRT) was performed as symptomatic therapy, and her symptoms were gradually relieved. The patient then developed two episodes of neutropenia associated with chemo-

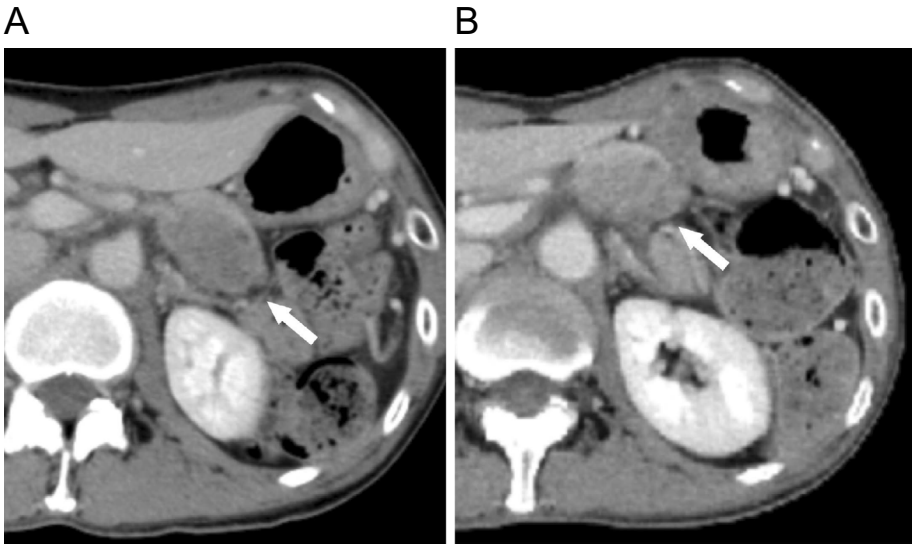

Figure 3. **Contrast-enhanced computed tomography (CT) before and after chemotherapy. (A) The maximum diameter of the pancreatic ductal carcinoma was 37 mm on contrast-enhanced CT before chemotherapy (arrow). (B) The maximum diameter of the pancreatic ductal carcinoma was 30 mm on contrast-enhanced CT after chemotherapy (arrow).**

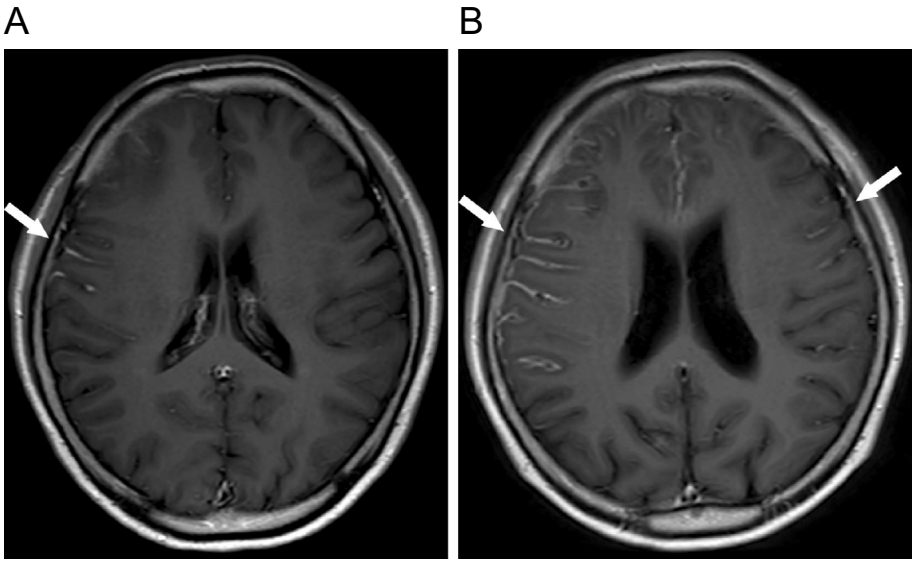

Figure 4. **Contrast-enhanced magnetic resonance imaging before and after chemotherapy. (A) Brain contrast-enhanced magnetic resonance imaging showed partial enhancement around the right cerebral leptomeninges before chemotherapy (arrow). (B) Widespread leptomeningeal carcinomatosis was observed from the right to left cerebral folia after chemotherapy (arrow).**

therapy. Therefore, the dosages of nab-PTX and GEM were reduced to 80% and 60%, respectively, from the second dose in the first cycle and first dose in the third cycle.

After three courses of chemotherapy, abdominal CT showed a slightly reduced mass volume of the PDAC (Fig. 3). However, brain MRI revealed widespread LMC from the right to left cerebral folia (Fig. 4). The carbohydrate antigen 19-9 level after the first, second, and third course of chemotherapy was 1,080 U/mL, 623 U/mL, and 1,613 U/mL, respectively. After the third course, the patient developed a consciousness impediment and left hearing impairment (Japan Coma Scale score of I-3) and was readmitted on an emergency basis (108 days after the first visit). Although neurogenic symptomatic therapy was promptly administered, the patient's consciousness level worsened, and she finally died 161 days after the first visit. A pathological autopsy revealed well-differentiated adenocarcinoma throughout a wide area of the bilateral leptomeninges. Brain parenchymal involvement was not detected (Fig. 5). Cancer tissue was not detected in the spinal pia mater. Well-differentiated tubular adenocarcinoma measuring 4 cm in size was identified in the pancreatic tail (Fig. 6). Apparent

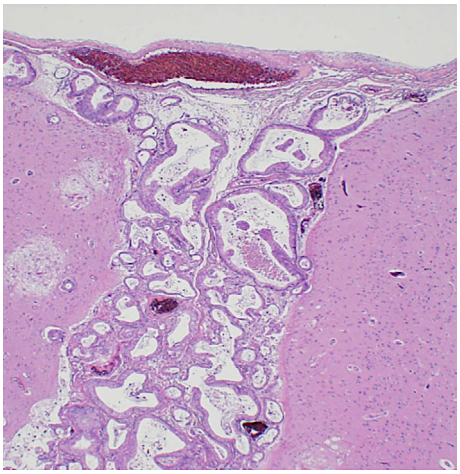

Figure 5. **A histological examination of the brain. Well-differentiated tubular adenocarcinoma was seen throughout a wide area of the leptomeninges, but no brain parenchymal involvement was detected.**

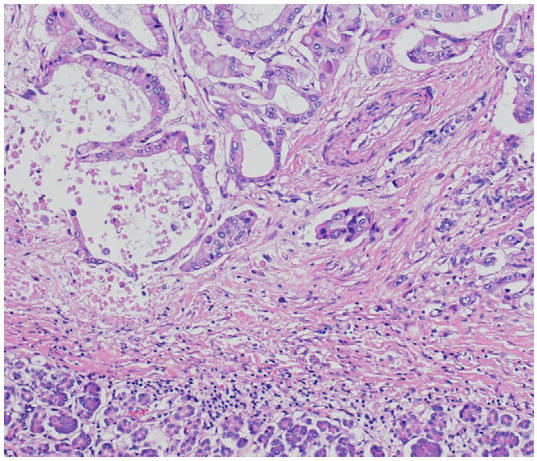

Figure 6. **A histological examination of the pancreas. Well-differentiated tubular adenocarcinoma similar to the cancer seen in the leptomeninges was identified in the pancreatic tail.**

damage of cancer cells or nests, which is regarded as a treatment effect, was not seen in either the primary PDAC lesion or leptomeninges. Additionally, several metastatic lymph nodules were detected, including the para-aorta lymph nodules, and a single liver metastasis with a diameter of 1 cm was detected in liver segment 4. Despite the inability to confirm the definitive diagnosis before treatment, LMC from PDAC was still suspected.

Discussion

Symptoms of LMC may include generalized findings such as headache and nausea, or patients may exhibit focal neurologic deficits that reflect the location of the involved leptomeninges, cranial neuropathies, and focal motor deficits (7). Symptomatic therapy is occasionally required for patients with LMC, and WBRT is commonly used. WBRT promptly provides significant palliation for neurogenic symptoms associated with CNS metastasis (27) and it was also effective for the patient's neurogenic symptoms in the present case. However, long-term toxicity induced by WBRT may cause dementia when WBRT is performed with chemotherapy (28). Therefore, the indications for WBRT in patients with a long-term prognosis should be carefully considered.

The diagnosis of LMC is confirmed by neuropathological examination of contrast-enhanced brain MRI and CSF analysis. Brain MRI shows leptomeningeal contrast enhancement, subependymal deposits, nodular enhancement, and hydrocephalus; these findings support the diagnosis (7). The definitive diagnosis is difficult in most patients because it requires the detection of malignant cells on CSF cytology obtained via lumbar puncture. Malignant cells are detected in the initial CSF sample in only 50% of patients with LMC (26). Thus, multiple lumbar punctures are sometimes required. Occasionally, the diagnosis must be confirmed comprehensively (e.g., MRI findings, existence of advanced cancer, and elevated tumor markers) if malignant cells are not detected.

Systemic chemotherapy is a common treatment for unresectable PDAC but it is generally regarded as ineffective for LMC because only a limited number of anticancer drugs have shown good intracerebral fluid transferability (29). Although the effectiveness of intrathecal chemotherapy for brain metastasis has been reported, the evidence level remains insufficient: only small case series have so far been published (30). Thus, systemic chemotherapy with good intracerebral fluid transferability is reasonable for the treatment of LMC from PDAC in daily clinical practice. Nevertheless, most patients with PDAC have already undergone several treatment regimens when LMC develops, and the available regimens are generally limited.

The combination of nab-PTX+GEM is widely used as the first-line regimen for unresectable PDAC (31). However, only one report has focused on the treatment outcomes for LMC from PDAC. In this report, Ceccon et al. (25) described a 51-year-old man with LMC from PDAC that responded to nab-PTX+GEM in terms of elimination of tumor cells from the CSF and concurrent long-term clinical improvement (3 months after diagnosis of LMC). The patient finally developed neurogenic disorders associated with LMC progression (palsies of cranial nerves, gait disorder, and severe consciousness impediment) and soon died.

In our case, the primary PDAC lesion decreased in size as it responded to nab-PTX+GEM. However, the LMC lesion spread widely throughout the cerebral folia. Although the patient finally died of LMC progression, her survival time exceeded that of most patients with LMC described to date (Table). This result might indicate that nab-PTX+GEM can provide a longer survival period than other regimens (e.g., thiotepa+methotrexate+cytarabine, methotrexate+cytarabine+gemcitabine, and pelareorep+carboplatin+paclitaxel) (11, 15, 19). However, nab-PTX+GEM seems to be

Table. **Reported Cases of Leptomeningeal Carcinomatosis from Pancreatic Ductal Adenocarcinoma.**

Reference	Age (y)/Sex	Chemotherapy	Radiotherapy	Survival
9	N.R./N.R.	N.R.	N.R.	N.R.
10	36/Male	No	No	Few weeks, not specified
11	49/Male	Thiotepa, methotrexate, cytarabine	No	8 weeks
12	55/Male	No	No	7 weeks
13	64/Male	Gemcitabine	Yes	168 weeks
14	44/Female	Methotrexate and intrathecal ^{125}IUdR	No	24 weeks
15	59/Male	Methotrexate, cytarabine, gemcitabine	No	6 weeks
16	72/Male	No	No	Few weeks, not specified
17	45/Female	No	No	Rapid death, not specified
18	57/Male	FOLFIRINOX	Yes	N.R.
19	72/Female	Pelareorep, carboplatin, paclitaxel	No	8 weeks
20	58/Female	No	No	1 week
21	80/Male	No	Yes	N.R.
22	58/Male	No	No	5 weeks
23	54/Male	Capecitabine, irinotecan, topotecan, bevacizumab	Yes	45 weeks
24	59/Male	No	No	2 weeks
25	51/Male	Nab-paclitaxel plus gemcitabine	No	12 weeks
Present case	59/Female	Nab-paclitaxel plus gemcitabine	Yes	23 weeks

N.R.: not reported, ^{125}IUdR: 5-iodo-2'-deoxyuridine labeled with 125-I, FOLFIRINOX: fluorouracil, leucovorin, irinotecan, and oxaliplatin

insufficient to suppress LMC progression because our patient eventually died of LMC progression, as did the patient described by Ceccon et al. (25). A possible reason for these outcomes might be the poor intracerebral fluid transferability of nab-PTX+GEM.

Nevertheless, nab-PTX+GEM appears to be a reasonable treatment. Previous reports have indicated that it seems to be a relatively effective regimen (9-25). Moreover, combinations of fluorouracil+leucovorin+irinotecan+oxaliplatin and erlotinib+gemcitabine are used as first-line regimens for unresectable PDAC, as with nab-PTX+GEM; however, no articles have described the treatment outcomes of these regimens for LMC from PDAC. If nab-PTX+GEM is administered for LMC from PDAC, then careful neurological examinations and frequent brain MRI scans are necessary to avoid missing a progression of LMC.

We herein described the treatment outcome of nab-PTX+GEM for LMC from PDAC. This case is extremely rare in terms of the development of LMC from PDAC without multi-organ metastasis at the initial presentation. The patient died of LMC progression despite control of the primary PDAC lesion by nab-PTX+GEM. An autopsy confirmed that the LMC progression was the cause of death. Thus, the difference in the treatment response to nab-PTX+GEM between the LMC from PDAC and the primary PDAC lesion was verified. The number of cases of CNS metastasis from PDAC is expected to continuingly increase with improvements in systemic therapies and longer survival times. Future similar case reports will hopefully continue to provide more information to improve the prognosis of CNS metastasis from PDAC.

The authors state that they have no Conflict of Interest (COI).

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