Leptomeningeal Carcinomatosis Originating from Advanced Gastric Cancer: A Report of Three Cases and Review of the Literatures

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Leptomeningeal Carcinomatosis Originating from Advanced Gastric Cancer—A Report of Three Cases and Review of the Literatures

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Abstract
Background: Leptomeningeal carcinomatosis (LMC) is a rare complication of gastric cancer.

Case 1. A 57-year-old female was diagnosed with gastric cancer and underwent distal gastrectomy with D2 lymph node dissection. Two years later, the patient suffered from para-aortic lymph node metastases and provided chemotherapy. During the chemotherapy, the patient emergently visited our hospital with chief complaints of a severe headache and dizziness. The above symptoms promptly abated by meningeal drainage, with a high value of the cerebrospinal fluid (CSF) pressure. Despite the administration of subsequent chemotherapy, the patient's clinical state rapidly worsened, including gradual progression of both blindness and hearing loss.

Case 2. A 42-year-old male was diagnosed with Stage IV gastric cancer due to both distant lymph node metastases and an ascites. Chemotherapy with S-1 plus docetaxel was initiated. Upon finishing the fifth course of treatment, the patient complained of a severe headache. The magnetic resonance imaging (MRI) findings were suggestive of LMC. Under suspicion of carcinomatous meningitis, the patient underwent both cerebrospinal drainage with a high pressure value of 180 mmH2O and a cytological examination with a diagnosis of Class V. Immediately following the cerebrospinal drainage, the patient's symptoms promptly diminished.

Case 3. A 66-year-old female was diagnosed with gastric cancer and underwent total gastrectomy with D2 dissection. About a year later, the patient suffered from the peritoneal dissemination, and provided serial chemotherapy regimens for 13 months. Thereafter the patient suffered from mildly stiff shoulders followed by serial severe headaches, and meningeal drainage was performed. The CSF showed pleocytosis and the presence of neoplastic cells, leading a diagnosis of LMC. After the placement of an Ommaya reservoir, the intrathecal chemotherapy was performed. Within two weeks of treatment, the patient's condition improved significantly, and the cell counts in the CSF obtained from the Ommaya reservoir remained low for six months after the first diagnosis of LMC.

Conclusions: Although gastric LMC-affected patients often exhibit a fatal clinical course, the administration of intrathecal chemotherapy may improve survival. Systemic chemotherapy may be also administered in a limited number of patients with a superior performance status. At present, each case requires the individual making treatment decisions. Further accumulation of clinical cases and improving the overall understanding of the pathogenesis of this disease is needed in order to advance in the treatment of gastric LMC.

Key words: Gastric cancer · Leptomeningeal carcinomatosis · Chemotherapy
**Introduction**

Several investigators have reported that metastatic leptomeningeal carcinomatosis (LMC) is estimated to occur in 3% to 8% of patients with solid cancer based on a large autopsy study. The most common causes of LMC are breast cancer, lung cancer, malignant melanoma, leukemia and large cell lymphoma. Gastric cancer rarely progresses to leptomeningeal involvement, with a reported incidence of only 0.17% to 0.19% of gastroesophageal cancers. The prognosis of patients with gastric LMC is very poor; the median survival time has been reported to be only several weeks. LMC is characterized by the diffuse spread of the cancer to the leptomeninges via the cerebrospinal fluid (CSF); therefore, the diagnosis is based on the presence of malignant cells in the CSF. The clinical status of LMC is difficult to diagnose, particularly as the first sign of a primary tumor. As the prognosis of patients with advanced cancer has been improved due to the development of chemotherapy, the incidence of cancer–associated secondary meningeal lesions has been increased within the last two decades.

In this article, we report three cases of LMC derived from gastric cancer and discuss the diagnosis and chemotherapy of this disease in the literature.

**Case report 1**

A 57-year-old female was diagnosed with gastric cancer at our hospital. She underwent distal gastrectomy with D2 lymph node dissection in December, 20XX, with a postoperative pathological stage of pT3 (SS), pN2, pP0, pH0, pCY0, fStage IIIA. The selection of the cancer stage was determined according to the criteria of the *Japanese Classification of Gastric Carcinoma* (14th edition). Despite the presence of the advanced lesion, the patient rejected postoperative adjuvant chemotherapy and instead received follow-up. In November 20XX + 2, she complained of dysphagia, and a computed tomography (CT) scan showed para-aortic lymph node metastases with a maximum of diameter of 110 mm. She provided informed consent to participate in a randomized clinical trial of recurrent gastric cancer, and 5-fluorouracil plus paclitaxel combination chemotherapy was administered with good compliance. 5-Fluorouracil was given at a dose of 500 mg/m² on days 1–5, and paclitaxel was given at a dose of 60 mg/m² on days 8, 15, and 22. The chemotherapy regimen was repeated every four weeks. After two courses of treatment were completed, a CT scan showed a partial response against the targeted tumor without any adverse events higher than grade 3 evaluated according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE ver. 3.0). During the third course of chemotherapy, on day 7, just after the administration of days 1–5 of 5-fluorouracil,
the patient emergently visited our hospital with chief complaints of a severe headache and dizziness. Under suspicion of meningitis, meningeal drainage was performed, with a high CSF pressure value of 580 mmH₂O, and the above symptoms promptly abated. Despite the administration of treatment with combination chemotherapy consisting of methotrexate and 5-fluorouracil, the patient’s clinical state rapidly worsened, including gradual progression of both blindness and hearing loss; she ultimately died without regaining these nervous functions. A cytological examination of the cerebrospinal fluid showed Class V adenocarcinoma with signet ring cells (Fig. 1a).

**Case report 2**

A 42-year-old male was diagnosed with gastric cancer at our hospital in July 20XX. He was diagnosed with cStage IV disease due to both distant lymph node metastases and a small volume of ascites on a CT scan. Combination chemotherapy with S-1 plus docetaxel was initiated before surgery on August 4th, 20XX and it was continued with good compliance. S-1 was given at a dose of 80 mg/m², was given on days 1–14, and docetaxel was given at a dose of 40 mg/m² was on day 1 for 120 minutes. The chemotherapy regimen was repeated every three weeks. CT scans were examined monthly to evaluate the presence of lymph node metastases in accordance with the RECIST criteria, and the results showed a partial response. The amount of ascites diminished, and the size of the primary carcinoma of the stomach decreased. Upon finishing the fifth course of treatment, the patient complained of a severe headache. The magnetic resonance imaging (MRI) findings were suggestive of LMC (Fig. 2). Under suspicion of carcinomatous meningitis, the patient underwent both cerebrospinal drainage with a high pressure value of 180 mmH₂O and a cytological examination and was hospitalized. The cerebrospinal fluid contained many cancer cells, with a diagnosis of Class V. The first round of chemotherapy failed due to progressive disease of the newly spreading gastric cancer, despite the fact that the regimen had been effective for the lymph node metastases and primary lesion in the stomach. Immediately following the cerebrospinal drainage, the patient’s symptoms promptly diminished. As sequential treatment, methotrexate plus 5-fluorouracil combination chemotherapy was administered. On day 2, he suffered from acute severe abdominal pain. A CT scan was performed emergently, which showed free peritoneal air. The patient underwent laparotomy and the perforated gastric cancer was found followed by bacterial peritonitis. Whole peritoneal lavage and primary closure of the perforated site with an omental patch were performed. The placement of an Ommaya reservoir for the delivery of chemotherapeutic agents was presented to the patient; however, he rejected progressive treatment and selected the best supportive care.

**Case report 3**

A 66-year-old female was diagnosed with gastric cancer at our hospital. She underwent total gastrectomy with D2 dissection in June 20XX (pT3, pN3, pPO, pHO, pCY0, fStage IIIIB). The patient was administered oral S-1 administration as adjuvant chemotherapy; however the treatment was discontinued due to an adverse event of

**Fig. 2** MRI findings in case 2. Fine linear enhancement in short segments of the brain surface was seen in the area of LMC, especially in the sagittal view (arrows 1–3).
severe nausea. Thereafter, she rejected further postoperative adjuvant chemotherapy and instead only received conservative follow-up. In September 20XX + 1, the patient visited our hospital with complaints of abdominal distension and dysphagia. A CT scan showed massive ascites and bilateral ovarian tumors. She provided informed consent to participate in a randomized clinical trial for recurrent gastric cancer and received S-1 plus docetaxel combination chemotherapy with good compliance. S-1 was given at a dose of 80 mg/m² on days 1–14, and docetaxel was given at a dose of 35 mg/m² on days 1 and 15 for 120 minutes. The chemotherapy regimen was repeated every four weeks. After two courses of treatment were completed, a CT scan showed a partial response against the targeting tumor without any adverse events higher than grade 3 evaluated according to the CTCAE ver. 3.0. The ascites promptly diminished. In January 20XX + 2, both serum carcinoembryonic antigen (CEA) and CA19–9 were found to be increased. A CT scan obtained in February 20XX + 2 showed an interval increase in the size of the ovarian tumors with a designation of progressive disease. The biweekly administration of irinotecan (at a dose of 150 mg/m²) was initiated as the second-line chemotherapy. A long-term partial response was obtained with this line of therapy. In October 20XX + 2, the patient suffered from mildly stiff shoulders followed by serial severe headaches. Under suspicion of meningitis, meningeal drainage was performed with a normal CSF pressure. However, the CSF showed pleocytosis and the presence of neoplastic cells, leading to a diagnosis of LMC (Fig. 1b). The placement of an Ommaya reservoir, which is the intraventricular catheter system for the delivery of drugs into the CSF, for treatment was presented to the patient, who accepted the procedure. Methotrexate was administered at a dose of 15 mg/body as the intrathecal chemotherapy. Within two weeks of treatment, the patient’s condition improved significantly, and the cell counts in the CSF obtained from the Ommaya reservoir remained low for six months after the first diagnosis of LMC. The patient was able to stay at home overnight.

**Discussion**

Leptomeningeal carcinomatosis (LMC) is defined as malignant infiltration of the pia mater and the arachnoid membrane. LMC is one of the most serious complications that can occur in cancer patients. Wasserstrom et al. reported that LMC is frequently detected in patients with leukemia, lymphoma and some solid tumors among Western patients diagnosed LMC, and that the most frequently encountered solid tumors are breast (12–34%), lung (14–29%) and melanoma (17–25%). Adenocarcinoma is histologically the predominant cause of LMC of solid neoplasms. Among solid tumors, LMC is observed more frequently in cases of disseminated and progressive disease. In contrast to these findings, gastric cancer has been reported to be the principal etiology of LMC in Asia. Several studies have reported that the majority of the patients with gastric LMC have an advanced stage of disease and Bormann type III or IV lesions macroscopically. Histopathologically, LMC patients exhibit diffuse-type, poorly differentiated or signet ring cell adenocarcinoma. Metastasis to the central nervous system is a very rare complication of gastric cancer, generally occurring in 0.16~0.69% of gastric cancer patients in general.

In 1971, Olson et al. reported that the primary manifestation was headache in 38% of cases, mental disturbances (i.e. dementia) in 24% of cases, and spinal nerve symptoms, such as backaches or radiculopathy in 22~24% of cases. A loss of visual acuity and diplopia are the most common cranial nerve symptoms. Table 1 shows the clinical presentations of LMC as reported previously. In our report, all patients suffered from severe headaches. In case 1, rapid progression of cranial nerve signs was observed during treatment with chemotherapy, despite the good objective response, which should be taken into
Diagnosing LMC is often difficult, as some of the clinical symptoms are nonspecific, and the disease itself is not always evident on imaging studies. Many researchers have reported that the ability to diagnose LMC is dismal\(^{15}\). MRI is commonly regarded as the imaging study of choice and has been used to investigate normal and abnormal meningeal enhancement, with an emphasis on meningeal carcinomatosis\(^{12-14}\). In case 2, MRI findings showing enhancement of the meninges were also useful for making a diagnosis, as shown in Table 2. However, the presence of malignant cells in the cerebrospinal fluid (CSF) is ultimately considered diagnostic for LMC. The sensitivity of this parameter remains suboptimal, and Yamada et al. recommend the following technique to minimize the incidence of a false-negative cytology of the CSF\(^{13,15}\): (1) a minimum of 10 ml of CSF should be withdrawn with each sample solely for the cytological analysis, (2) the specimens must be processed promptly, including immediate fixation in ethanol-based fixative for cytology, (3) the CSF should be obtained from a site of known leptomeningeal disease (i.e., intraventricularly or via cervical spine puncture under fluoroscopic control in patients with cranial symptoms and LP in patients with spinal root dysfunction) and (4) the ventricular puncture or LP should be repeated if the initial cytology is negative but clinical suspicion is high which may help to improve the sensitivity of cytology.

Intrathecal chemotherapy is often used to treat LMC. Many investigators have reported that this chemotherapeutic approach might improve survival in the small scale trials\(^{17-19}\). However, the therapeutic benefits of intrathecal chemotherapy remain under discussion, primarily because no consistent survival benefits have been demonstrated. As chemotherapeutic agents, cytosine arabinoside (ara-C), methotrexate and thiotepa are most commonly employed to treat LMC in patients with gastric cancer\(^{16,24}\). Among these agents, methotrexate is the most frequently used\(^{18,19}\). In case 3, methotrexate was administered through the Ommaya reservoir, which improved the patient’s quality of life. In recent reviews and case reports, patients presenting with HER2-overexpressing metastatic breast cancer and suffering from LMC have been treated with trastuzumab directed to HER2 via intrathecal administration, with clinical improvements\(^{24,25}\). As trastuzumab in combination with chemotherapy can be considered a new standard treatment option in patients with HER2-overexpressing advanced gastric or gastro-esophageal junction cancer based on a phase III trial\(^{26}\), the intrathecal application of trastuzumab may provide an interesting therapeutic approach in patients with HER2-positive gastric cancer.

In summary, LMC is a rare but devastating complication of gastric cancer. Although affected patients often exhibit a fatal clinical course, the administration of intrathecal chemotherapy may

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\(^{*}\)Rizvi et al., 2011 [6]; Yamada et al., 2008 [15]
improve survival. Systemic chemotherapy may be also administered in a limited number of patients with a superior performance status. At present, each case requires the individual making treatment decisions. Improving the overall understanding of the pathogenesis of this disease and the subsequent impairment of the blood–brain barrier is therefore needed in order to advance in the treatment of gastric LMC.

References


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胃癌髄膜癌腫症の3例

3例の胃癌髄膜癌腫症を報告する。症例1は50歳、男性。胃癌の診断で胃側胃切断術施行された2年後に脳干動脈リな節転移に再発を来たし5-FU + paclitaxelによる一次化学療法を開始した。治療開始中に頭痛と眩暈が出現し、細胞診を含む精査の結果、髄腔癌（580mmH₂O）を伴う髄膜癌腫症と診断された。髄液ドレナージにて症状は改善したが、一次治療はPDと判断し、二次治療としてmethotrexate + 5-FUに移行した。しかしど病勢は急激に進行し、全盲および聴覚障害に至った。症例2は40歳、男性。腹膜播種と遠隔リな節転移を伴うStage IV胃癌に対してS-1 + docetaxelによる化学療法施行中であったが、5コース終了後に激しい頭痛が出現した。MRI上、脳実質表面の髄膜の異常増強所見から髄膜癌腫症が疑われ、髄液細胞診および髄腔圧力（180mmH₂O）にて診断確定に至った。髄液ドレナージにて症状は改善したが、その後再発症状の穿孔による汎発性腹膜炎を発症した。症例3は60歳、女性。胃癌の診断で胃全摘術を施行され、術後補助化学療法是有害事象で早期に中止されていた。術後1年3ヶ月で腹膜播種再発を来たし、S-1 + docetaxelによる一次治療、化学療法開始5ヶ月後からirinotecanによる二次治療が施行されていた。治療開始後1年1ヶ月の時点でPRであったが、同時期に両肩の強さに引き続き激しい頭痛を訴え、髄膜癌腫症とされ、髄腔圧は正常であったが、髄液ドレナージにて症状は軽快し、髄液細胞診にてClass Vであった。二次治療PDかつ癌性髄膜炎の診断で、Ommayaリザーバーを留置してmethotrexateによる髄腔内化学療法を開始したところ、症状は改善し、約6ヶ月間、同治療を続ける可能であった。