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Case Report

Leptomeningeal Carcinomatosis From Gallbladder Cancer After Curative Resection: A Case Report and Review of Literature

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Introduction: Only 12 cases of gallbladder (GB) cancer associated with leptomeningeal carcinomatosis (LMC) have been reported so far. Herein, we report the first known case of LMC originating from GB cancer after curative resection and discuss the risk factors of LMC associated with GB cancer.

Case Presentation: An 85-year-old Japanese woman presented with vomiting and impaired awareness 2 years after curative extended cholecystectomy for GB cancer. Computed tomography showed hydronephrosis of the right kidney and ureteral thickening. Magnetic resonance imaging revealed areas of hyperintense reflecting lesions along the cerebral sulci, suggesting meningitis. A spinal tap showed an elevated cerebrospinal fluid pressure of >270 mmH_2O and cytologic examination of the spinal fluid revealed the presence of adenocarcinoma cells. The patient was diagnosed with retroperitoneal metastasis and LMC originating from GB cancer. The patient was given palliative care and died 4 weeks after the onset of symptoms.

Conclusion: The findings of this study show that LMC could occur even after curative resection of GB cancer and should be considered when patients present with neurologic

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symptoms. Retroperitoneal metastases and poorly differentiated tumors are possible risk factors of LMC originating from GB cancer.

Key words: Leptomeningeal carcinomatosis – Gallbladder cancer – Rretroperitoneal metastasis – Poorly differentiated tumor

Leptomeningeal carcinomatosis (LMC) is a rare metastatic complication of gallbladder (GB) cancer. The common causes of solid tumor-related LMC are breast cancer, lung cancer, and melanoma.[1] Only 12 cases of GB cancer associated with LMC have been reported in the literature. Furthermore, LMC after curative resection has not been reported. A rare case of LMC from GB cancer after curative resection is reported herein, and the risk factors of LMC associated with GB cancer are discussed.

Case Presentation

An 85-year-old Japanese woman presented with vomiting and impaired consciousness 2 years after undergoing extended cholecystectomy with para-pancreatic lymph node dissection for the GB cancer. The resected GB tumor was a 75 × 60 mm flat-infiltrating tumor whose surface was covered by papillary extension (Fig. 1a). Histopathologic examination showed well-differentiated and poorly differentiated adenocarcinomas invading the subserosal layer (Fig. 1b–d). Mild lymphatic invasion was detected, but lymph node metastases were not detected. All surgical margins were cancer free. The tumor was classified as pT2bN0M0, pStageIIB in accordance with the Union for International Cancer Control TNM staging system (eighth edition). The patient was cancer-free and did not

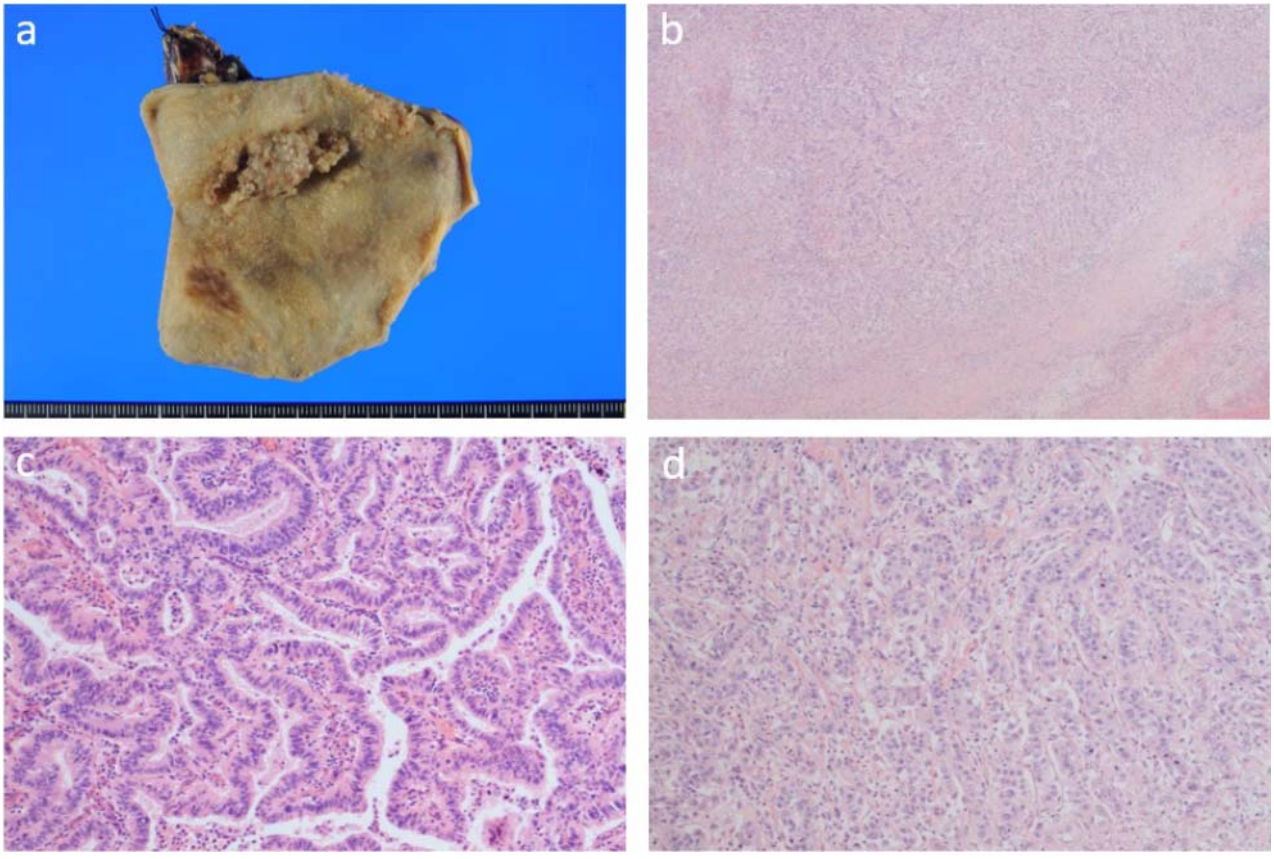

Fig. 1 Histopathologic findings. (a) A flat-infiltrating tumor covered with papillary expansions is shown. (b) Cancer cells are shown invading the subserosal layer (hematoxylin and eosin, ×40). (c) Components of well-differentiated adenocarcinoma are shown (hematoxylin and eosin, ×200). (d) Components of poorly differentiated adenocarcinoma are visible (hematoxylin and eosin, ×200).

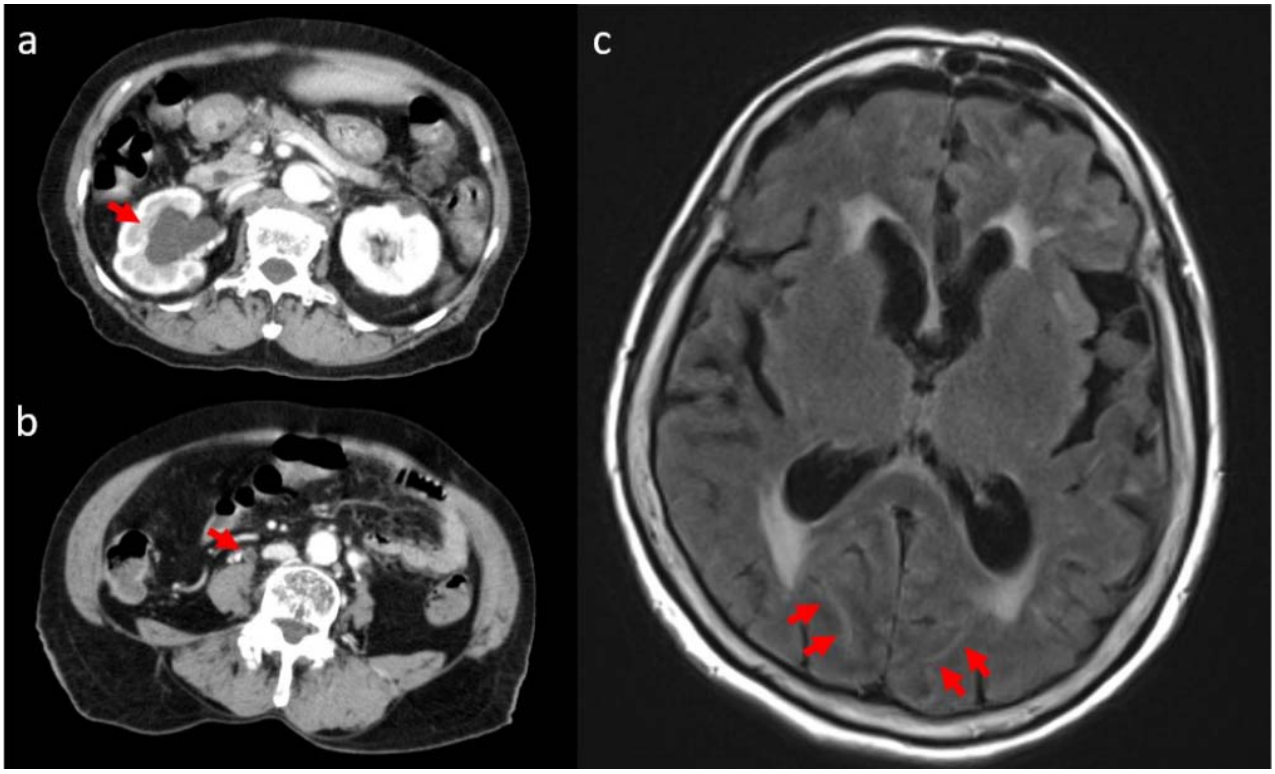

Fig. 2 Imaging findings. (a, b) Computed tomography shows hydronephrosis in the right kidney (arrow in a) and ureteral thickening (arrow in b). (c) Magnetic resonance imaging of the brain shows hyperintense areas of lesions along the cerebral sulcus (arrows).

require postoperative adjuvant chemotherapy for 2 years. However, on readmission, her Glasgow Coma Scale was E3V4M6 (13/15). Systemic computed tomography (CT) showed hydronephrosis of the right kidney and ureteral thickening (Fig. 2a, b). Magnetic resonance imaging (MRI) of the brain showed areas of hyperintense reflecting lesions along the cerebral sulci, suggestive of meningitis (Fig. 2c). A spinal tap showed increased cerebrospinal fluid (CSF) pressure of >270 mmH_2O. Cytologic examination of the CSF revealed the presence of adenocarcinoma cells (Fig. 3). Carcinoembryonic antigen (CEA) levels were elevated at 18.3 ng/mL (normal value, <4.5 ng/mL), but carbohydrate antigen (CA) 19-9 level was within the normal range. Cytologic examination of the patient's urine was negative for malignancy. Endoscopic and radiologic findings did not indicate any signs of malignancy. Therefore, the patient was diagnosed with retroperitoneal metastasis and LMC originating from the GB. She died 4 weeks after the initial presentation without further treatment.

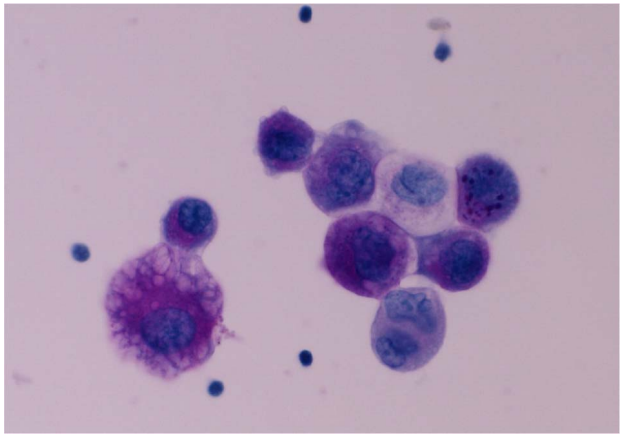

Fig. 3 Cytologic findings. Cytology of cerebrospinal fluid shows adenocarcinoma cells (Papanicolaou ×400).

Discussion

LMC occurs in 5%–8% of patients with solid tumors.[2] The most common solid tumors associated with LMC are breast cancer (12%–35%), lung cancer (10%–26%), and melanoma (5%–25%).[1] In East Asia, gastric cancer has been reported to be the principal etiology of LMC.[3,4] Thus far, only 12 cases of LMC

originating from GB cancer have been reported in the literature.[5–15] Furthermore, no cases of LMC after curative resection have been reported. LMC results in variable clinical presentations. The common symptoms are radicular pain, cranial nerve deficits, headache, back pain, visual impairments, hearing loss, and neurocognitive syndromes.[16] During advanced stages, symptoms caused by elevated intracranial pressure include headaches, nausea or vomiting, and somnolence appear.[16] According to the National Comprehensive Cancer Network Guidelines for Central Nervous System Cancers, a diagnosis of LMC can be made if one of the following diagnostic criteria is positive: presence of tumor cells in the CSF, positive radiologic findings with supportive clinical findings, or signs and CSF symptoms suggestive of or positive for malignancy (high white blood cell count, low glucose level, and elevated protein level) in a patient known to have cancer.[17] If CSF cytology is negative for tumor cells, a second lumbar puncture should be considered. The positive rate of confirmed malignancy using CSF cytology is >50% from the first tap;[18] however, it may increase to approximately >90% in the second tap.[19] MRI is reported to be a useful modality for LMC detection. MRI was found to have higher sensitivity and specificity in LMC detection than contrast-enhanced CT.[20] Positron emission tomography (PET) may be an alternative imaging modality for diagnosing LMC in patients who are unable to undergo MRI and or a spinal tap or in cases where initial MRI and or CSF cytology were negative for LMC.[21] Therefore, in a case of suspected LMC, cranial or spinal MRI and a spinal tap should be performed. In the present case, positive CSF cytology and MRI findings met the LMC diagnosis criteria. In 11 of the 12 previously reported cases,[5–15] LMC was diagnosed by performing CSF cytology (Table 1).

Treatments of LMC are limited and often ineffective, mostly due to limitations imposed by the blood-brain barrier and the extremely aggressive nature of this disease. Most untreated patients with LMC die within 4–6 weeks after diagnosis.[22] The median survival time has increased to 13–25 weeks due to various treatments, such as intraventricular and intrathecal chemotherapy.[23] In previously reported cases,[5–15] 7 untreated patients died within 2–10 weeks, while 6 treated patients died within 9–24 weeks (Table 1).

The pathways by which neoplastic cells reach the meninges are unknown. Proposed routes include the Batson venous plexus of paravertebral veins, arterial circulation, direct extension along perineural spaces, or paradoxical embolization.[24] Metastases in or near the vertebrae act as an intermediate station for tumor cells before they are further propagated into the central nervous system.[24] In the present case, metastasis in the retroperitoneal space was the only metastatic site except for LMC. It is hypothesized that tumor cells in the retroperitoneal space may have reached the meninges through the paravertebral Batson venous plexus or directly along perineural invasion. In 9 of the 12 previously reported cases,[5–15] metastatic lesions were found in the retroperitoneal space (Table 1). Therefore, Retroperitoneal metastases may be risk factors of LMC originating from GB cancer.

The question arises as to how the tumor cells reached the right ureter in the retroperitoneal space. We hypothesized that the right ureter was exposed when the Kocher manoeuvre was conducted during parapancreatic lymph node dissection. In GB cancer, tumor cells can be detected in the biliary juice in the bile duct even though the tumor is localized within the GB.[25] In the present case, the patient developed biliary leakages that required multiple suturing repairs during liver parenchymal dissection. Tumor cells in the bile juice might have spread to the retroperitoneal space around the right ureter from the injured bile duct. Therefore, careful attention should be paid to bile leakage resulting not only from a GB injury, but also from a liver parenchymal dissection during extended cholecystectomy.

Poorly differentiated adenocarcinoma is a rare primary GB cancer. Nevertheless, 7 of the 13 cases with LMC originating from GB cancer, including the present case, showed signet ring cells and mucinous or poorly differentiated adenocarcinomas (Table 1). In cases of gastric cancer, 94% of the LMC cases were poorly differentiated adenocarcinomas.[26] Therefore, poorly differentiated tumor types may be risk factors of LMC originating from GB cancer.

Conclusion

When patients have neurologic symptoms, even after curative resection of GB cancer, the possibility of LMC should be considered. Retroperitoneal metastases and poorly differentiated tumors are possible risk factors of LMC originating from GB cancer.

Table 1 LMC originating from GB cancer

Case	Author	Age	Sex	Treatment of GBC	Symptoms of LMC	Diagnosis of LMC	Treatment of LMC	Prognosis	Other metastasis	Tumor differentiation
1	Naylor AR (1988)	71	M	N/A	Headache Vomiting Anorexia	CSF cytology Post-mortem biopsy	Intrathecal chemotherapy	25 weeks, dead	Direct liver invasion Direct retroperitoneal invasion*	Signet-ring cell carcinoma #
2	Honma K (1990)	57	F	N/A	Lumbago Anuria General malaise Loss of appetite	CSF cytology Post-mortem biopsy	None	10 weeks, dead	Vertebral column* Systemic lymph nodes* Ureters* Common bile duct Pancreas*	Poorly differentiated adenocarcinoma with focal signet-ring cell carcinoma #
3	Pedrazzoli P (1992)	61	F	N/A	Pain in the muscles of legs Difficulty in standing	CSF cytology MRI	None	9 weeks, dead	Direct quadrate lobe of the liver Lymph nodes posterior to the pancreatic head*	N/A
4	Tans RJ (1993)	60	F	N/A	Diplopia Unsteady walking	CSF cytology	Intraventricular chemotherapy	11 weeks, dead	Liver Adrenal gland*	Well differentiated adenocarcinoma
5	Guamann (1999)	78	M	N/A	Headache Dysartheria Visual disturbance Paresis of tongue	CSF cytology MRI Post-mortem biopsy	Intrathecal chemotherapy	9 weeks, dead	Hepatoduodenal ligament	Poorly differentiated adenocarcinoma with focal signet-ring cell carcinoma #
6	Glosova (2003)	58	F	N/A	Headache Seizure Coma	CSF cytology Post-mortem biopsy	None	3 weeks, dead	Regional and lumbar lymph nodes* Peritoneal and pleural dissemination	Mucinous carcinoma with focal signet-ring cell carcinoma #
7	Miyagui T (2003)	43	F	N/A	Headache Agitation	Post-mortem biopsy	None	6 weeks, dead	Systemic lymph nodes* Ovaries Vertebral column* Pulmonary arteries	Moderately differentiated adenocarcinoma with focal mucinous carcinoma #
8	Goyal S (2014)	54	F	Cholecys-tectomy RT	Low back pain Loss of vision Multiple joint pain Headache	CSF cytology	Palliative whole brain radiation Steroids and diuretics	No follow-up	Multiple paraaortic lymph nodes*	Well differentiated adenocarcinoma
9	Doval DC (2015)	58	F	GC	Occipital headache Vomiting	CSF cytology MRI	None	No follow-up	Systemic lymph nodes*	N/A
10	Doval DC (2015)	50	M	GC	Headache Back pain	CSF cytology MRI	None	No follow-up	Multiple retroperitoneal nodes*	N/A
11	Jose N (2017)	55	M	N/A	Headache Vomiting	CSF cytology	Palliative VP shunt	*N/A*	Direct liver invasion	Signet-ring cell carcinoma #
12	Khan TH (2017)	67	F	GC	Headache Difficulty speaking Confusion Lethargy	CSF cytology MRI	Palliative whole brain radiation Steroids and diuretics	No follow-up	N/A	N/A
13	Present case	86	M	Cholecys-tectomy	Vomiting	CSF cytology MRI	None	4 weeks, dead	Retroperitoneal space*	Well and poorly differentiated adenocarcinoma #

GC, gemcitabine and cisplatin; N/A, not available; #, poorly differentiated tumor; RT, radiation therapy; *, retroperitoneal metastasis.

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