J Gastrointest Canc (2019) 50:315–319
DOI 10.1007/s12029-017-0004-0

CASE REPORT

Leptomeningeal Carcinomatosis Associated with Gall Bladder Carcinoma: a Case Report and Review of Literature

Talal H. Khan[1] · Manik Veer[1] · Mohammad Bilal[1] · Sheilah Curran-Melendez[2] · Prashant M. Jani[3] · Gregory S. Long[3]

Published online: 15 September 2017

Introduction

Gallbladder carcinoma (GBC) is the most common malignancy of the biliary tract and ranks sixth amongst gastrointestinal cancers [1]. Despite these statistics, it is an uncommon disease with a highly variable prevalence amongst certain indigenous populations [1]. GBC has a poor prognosis beyond initial stages [1]. En bloc hepatic resection of segments IVB and V with lymphadenectomy in early stages of resectable GBC represents the only chance for a cure; however, recurrence rates have been reported to be very high [1, 2]. Chemotherapeutic options include gemcitabine in combination with cisplatin or fluoropyrimidine-based regimens [2]. The most common site of metastasis for GBC is the liver, while involvement of the leptomeninges is extremely rare [1, 2].

We present a case of stage IV gallbladder carcinoma (GBC) with leptomeningeal involvement. A thorough literature review identified less than 15 cases of leptomeningeal disease with GBC.

Methods

We conducted a literature review of PubMed with keywords as follows: "Leptomeningeal Carcinomatosis," "Meningeal Carcinomatosis," "Leptomeningeal spread," "Leptomeningeal Carcinomatosis AND gallbladder carcinoma," "Leptomeningeal Carcinomatosis AND gallbladder cancer," "leptomeningeal carcinomatosis AND solid tumors OR solid malignancy," "gallbladder carcinoma AND management," "Leptomeningeal carcinomatosis AND management," "leptomeningeal carciomatosis AND diagnosis," "leptomeningeal carcinomatosis AND CSF analysis," "Leptomeningeal carcinomatosis AND prognostic factors." We also performed a search on Google Scholar with the same keywords.

Case Report

A 67-year-old Caucasian female, initially diagnosed with gallbladder carcinoma 16 months prior to admission presented to the hospital with 2 days of difficulty speaking, confusion, and lethargy. The patient was status post-chemotherapy with gemcitabine and cisplatin, and last chemotherapy administration was 3 months prior to presentation. On presentation, the patient's family reported intermittent headache for 4 weeks. The patient was not following commands. Her Karnofsky score was 50. On exam, her blood pressure was 186/94 mmHg, heart rate was 70 beats per minute, temperature was 37.7 degrees Celsius and respiratory rate was 18 breaths per minute. On neurological exam, cranial nerves were intact, her muscle strength in the right upper extremity, right lower extremity and left lower extremity was 5/5 and 3/5 in her left upper extremity. The patient withdrew her left upper extremity to pain; there was no pronator drift. Sensation was equal and symmetrical in bilateral upper and lower extremities. Motor reflexes were normal in all extremities. Her laboratory values were as follows: hemoglobin 11.9 g/dL (normal, 12–16 g/dL), platelet count 92,000 mm^3 (normal, 150,000–400,000 mm^3), white blood cell count 7.28 × 10^9/L (normal, 4.5–10.5 × 10^9/

✉ Mohammad Bilal
billa17@hotmail.com

[1] Department of Internal Medicine, Allegheny General Hospital, 320 East North Ave, Pittsburgh, PA 15212, USA

[2] Department of Radiology, Allegheny General Hospital, Pittsburgh, PA, USA

[3] Department of Hematology and Oncology, Allegheny General Hospital, Pittsburgh, PA, USA

L), serum blood urea nitrogen 19 mg/dL (normal, 8–25 mg/dL), serum creatinine 0.63 mg/dL (normal, 0.6–1.4 mg/dL). A CT scan of the head without contrast did not reveal any acute infarction, mass effect, or hemorrhage. MRI of the brain with contrast revealed leptomeningeal enhancement (nodular type) which was most pronounced in the cerebellum, quadrigeminal plate cistern and bilateral occipital lobes. [Fig. 1] A lumbar puncture was performed, which showed high protein (244 mg/dL), low glucose (39 mg/dL), and high WBCs (315/mcL). Due to concerns for infection, the patient was started on broad spectrum antibiotics (intra-venous vancomycin, ceftriaxone, and acyclovir); however, cytology confirmed malignant cells consistent with adenocarcinoma. Cytokeratin stain and leukocyte antigen stain (LCA) were positive confirming a diagnosis of leptomeningeal carcinomatosis secondary to GBC [Fig. 2]. A repeat lumbar puncture was performed which confirmed the findings [Table 1].

Antibiotics were discontinued and the patient was started on therapy with intravenous steroids and mannitol. Palliative whole brain radiation therapy (WBRT) was started and patient received 2 fractions of the total 5 cycles without any improvement in neurological function. At that time, the decision was made to stop further therapy and the patient was transferred to hospice services.

Discussion

Biliary tree cancers include gallbladder carcinoma and cholangiocarcinomas [3]. These diseases are more common in parts of Asia and have a possible association with liver flukes such as *Opisthorchis viverrini*, Opisthorchis felineus, and *Clonorchis sinensis* [3]. The therapy for these cancers involves surgical resection with a 5-year survival ranging between 8 and 40% [3]. Despite surgery, recurrence is common and data regarding adjuvant therapy is limited [3]. Only one phase 3 trial, Advanced Biliary Cancer 02 trial showed some benefit in progression-free survival with combination of gemcitabine plus cisplatin [4]. Complicating the picture is the fact that diagnosis usually takes place in advanced disease, more commonly when the disease is not amenable to surgery [1, 2]. Leptomeningeal carcinomatosis (LMC) is exceedingly rare in biliary tree cancers and reported only in a few case reports [5].

LMC constitutes involvement of the cerebrospinal fluid (CSF), pia, and arachnoid layers by a malignant process [6]. The spread may occur through paravertebral venous plexus of Batson, arterial circulation, direct extension along perineural spaces, or paradoxical embolization [7]. LMC may be seen in 5–8% of breast cancer cases, 6–18% cases of malignant melanomas, and 9–25% of lung cancers [6]. To the best of our knowledge, there have only been a few cases of LMC secondary to GBC reported thus far [Table 2]. There are 2 types of LMC described. The nodular type is associated with leptomeningeal tumor nodules that are contrast enhancing and the second diffuse non-adhering type characterized by non-adhering, free floating cells [6]. There is scant data comparing overall survival and/or disease-free survival between the adherent and non-adherent types of LMC. The distinction is primarily made on the basis of microscopic exam of the CSF. From a management standpoint, the nodular type LMC is more responsive to systemic chemotherapy as compared to intra-thecal chemotherapy.

Symptoms of LMC are variable and include radicular pain, headaches, paresthesia, cranial nerve palsies, cerebellar dysfunction, and alterations in mental status [6]. Diagnosis of LMC requires a combination of clinical suspicion, neuroimaging with MRI brain, and a lumbar puncture (LP) [6]. It is recommended that MRI be carried out prior to a LP as the procedure itself can cause some meningeal enhancement [6]. Typical MRI enhancement may be seen in up to 80% of the cases. Carcinoma cells in the CSF are diagnostic, with the

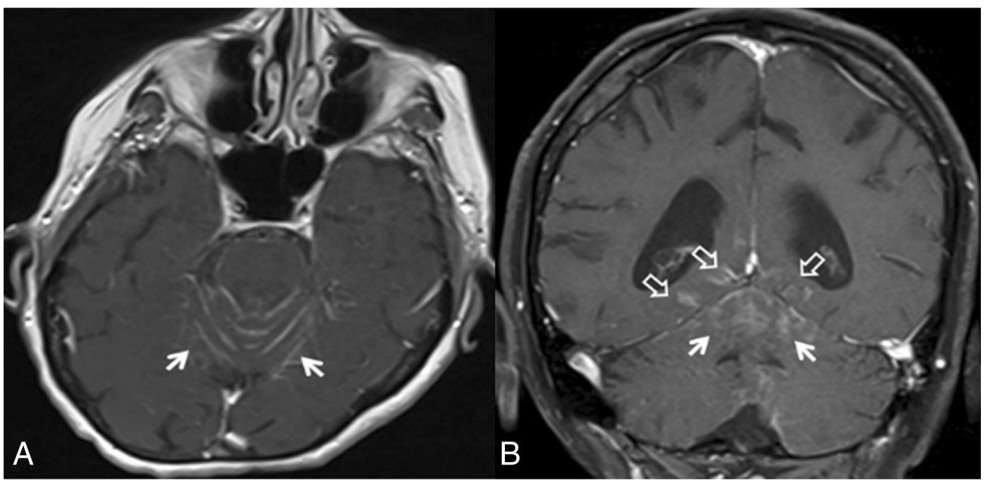

Fig. 1 T1-weighed post contrast imaging of the brain in axial (**a**) and coronal (**b**) demonstrates abnormal leptomeningeal enhancement overlying the cerebellar folla (solid arrows) and the bilateral parasagittal occipital lobes (open arrows)

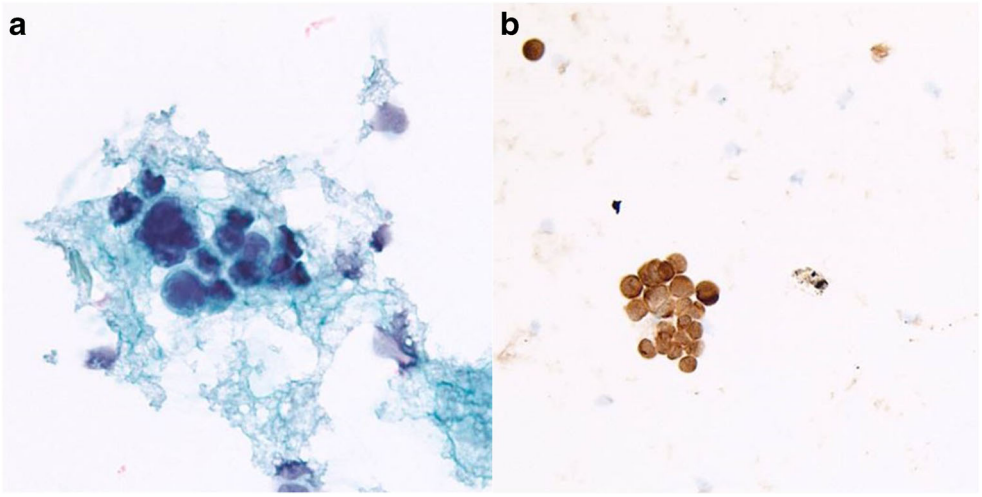

Fig. 2 CSF cytology. The CSF cytology showed the presence of large neoplastic cells with hyperchromatic nuclei and high N/C ratio (**a**). The neoplastic cells were positive for cytokeratin immunocytochemical staining (**b**)

exception of a few false-positive results in patients who have reactive lymphocytes (which are difficult to distinguish from malignant lymphomatous cells) because of an infectious or inflammatory process in the CSF. However, negative cytologic findings do not rule out the diagnosis, as 50% of patients with LC have a negative cytologic result on the first LP. If further confirmation is needed, an initial LP may have a positive yield in 70–90% and this increases to 85–90% on repeat LP if the first one is found to be non-diagnostic [6]. Tumor marker levels including CEA, CYRFA 21-1, and PSA are also helpful in cases with LMC due to lung or prostate cancer, but no specific tumor markers are available for GBC.

There continues to be a paucity of literature for therapeutic options in LMC [17]. A multidisciplinary, patient-centered approach is essential with the understanding that despite therapy, survival is guarded and ranges between 3 and 6 months [6]. To facilitate patient-centered discussions, the National Comprehensive Cancer Network (NCCN) poor prognostic indicators may be used [6] [Table 3].

Therapeutic options for both types of LMC include intracranial implantation of reservoirs for intrathecal chemotherapy administration, ventriculoperitoneal shunts, radiation therapy (RT), and systemic chemotherapy [6]. Intrathecal chemotherapy regimens include high-dose methotrexate, cytarabine, and thiotepa for LMC associated with solid tumors. However, these regimens cannot be used for noduar disease [18, 19]. The evidence for use of systemic chemotherapy in nodular-type LMC stems from retrospective case series showing some improved survival [6, 20]. WBRT provides rapid symptomatic control, restoration of CSF flow secondary to obstruction but is not known to increase survival and hence is reserved for palliation [21].

Some common features of prior LMC associated with GBC cases include rapid neurological decline and absence of use of systemic chemotherapy. Seven out of ten cases [Table 2] do not report primary GBC at the time of presentation with neurological symptoms, pointing to the insidious nature of GBC. LMC was reported more commonly in females and diagnosis was confirmed via LP and histopathology. Survival was reported for 6 cases and averaged at 53 days which is in line with general survival for LMC. Only one of the reported cases was treated with surgery and a time to development reported at 6 years. This is consistent with reported literature of survival for gall bladder cancers [3]. This indicates that surgically resected GBCs may not progress to LMC. Furthermore, average survival of 53 days indicates that GBC-associated LMC is not very different from other causes of LMC.

Our literature review confirmed that despite the availability of various therapeutic options, there is a lack of standardization in therapy for LMC with generally poor outcome. This is mainly due to the fact that prognostic factors differ in each individual patient. There needs to be a multi-disciplinary

Table 1 Findings on CSF from lumbar punctures

Lumbar puncture	Cell count	Total protein	Glucose	PAS stain	Leukocyte common antigen (LCA)	Cytokeratin (CK)
1	315/μL	244 mg/dL	39 mg/dL	+	+	+
2	21/μL	229 mg/dL	39 mg/dL	+	+	+

Table 2 Comparison of important characteristics noted in analyzed case reports citing GBC's association with LMC

Case	Age/Sex	Diagnosis(Dx) of GBC	Therapy for GBC	Months to LMC diagnosis	Type of LMC	Symptoms*	Mode of Dx	Therapy for LMC	Survival#
Our Case	67/F	08/2014	Non-surgical; G + C	16	Nodular	AMS, aphasia, CN-VII palsy	MRI Brain; + LP	Partial WBRT; supportive care$	Tx to hospice; no follow-up
1[8].	58/F	10/2011	Non-surgical; G + C	3	Diffuse	Occipital HA, projectile vomiting	MRI Brain; + LP	None reported; N/A	Tx to hospice. No follow-up
2[8].	50/M	02/2012	Non-surgical; G + C	3	Mixed	HA	MRI Brain; +LP	None reported	Tx home. No follow-up
3[9].	61/F	Undiagnosed at presentation	N/A	N/A	Nodular	LMN involvement of UE & LE	MRI Brain; +LP	None reported	63 days PP
4[10]	60/F	Undiagnosed at presentation; ID at autopsy	N/A	N/A	N/A	Diplopia; ataxia	+LP	IT MTX via Ommaya reservoir	75 days PP
5[11].	78/F	Undiagnosed at presentation	N/A	N/A	N/A	HA, diplopia, dysarthria, dysphagia, CNXII palsy	MRI Brain; +LP	IT MTX, unknown whether via VP shunt or reservoir	9 weeks PP
6[12].	54/F	6 years before Dx of LMC	Radical cholecystectomy + ART; No Chemo	72	N/A	Painless visual loss, back pain, HA	+LP w/ -ve LCA and +CK	Palliative WBRT; supportive care$	Tx to hospice. No follow-up
7[13].	43/F	Undiagnosed at presentation; ID at autopsy and co-presented w/Krukenberg tumor	N/A	N/A	Diffuse	AMS; CN palsy; nuchal rigidity; seizures	PM biopsy	None	2–3 weeks PP
8[14].	57/F	Undiagnosed at presentation; ID at autopsy	N/A	N/A	Diffuse	Back pain	+LP; PM biopsy	None	~2 ½ months PP
9[15].	58/F	Undiagnosed at presentation; ID at autopsy	N/A	N/A	N/A	HA, seizures	+LP; PM biopsy	None	3 weeks PP
10[16]	55/M	Undiagnosed at presentation	Palliative	N/A	N/A	HA, CN 6th Palsy	+LP	Palliative; VP shunt for symptomatic relief	Transfer to home; No follow-up

Key: *Dx* diagnosis, *PC* personal characteristics, *Tx* transfer, *PP* post-presentation with symptoms, *HA* headaches, *CN* cranial n., *WBRT* whole brain radiation therapy, *G + C* gemcitabine + cisplatin chemotherapy regimen, *PM* post-mortem, *+LP*, +ve CSF cytology for malignant cells, *AMS* altered mental status, *ART* adjunctive radiation therapy, *BM* additional parenchymal brain metastases +, present or -, absent, *IT* intrathecal, *MTX* methotrexate, * Initial symptoms that prompted a neurological evaluation; # Duration of survival after initial presentation (does not include parameters for quality of life, morbidity etc.); $ Systemic steroids, diuretics including mannitol, IVFs

Table 3 Predictors of poor prognosis

U.S National Comprehensive Cancer Network (NCCN) poor prognosis group
Karnofsky Index <60–70%
Severe Neurological deficits
Large tumor burden with low likelihood of response to systemic chemotherapy
Presence of brain parenchymal metastasis
Obstruction of CSF flow

approach for these patients with involvement of oncology, neuro-oncology, radiation oncology, neurosurgery, and palliative medicine. Future studies looking at the efficacy of various therapies available, keeping in view the prognostication of patients with an algorithmic approach that are tailored to achieve the best possible outcomes for these terminally ill patients, are needed.

Author Contributions TK drafted the manuscript and performed literature search. MV and GL were involved in the care of patient and provided important edits. MB edited the manuscript and performed literature search. SCM provided important input on radiological findings and significance. GL provided expert opinion on the manuscript.

Compliance with Ethical Standards

Consent Informed consent was obtained.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clinical epidemiology. 2014;6:99–109.
2. Zhu AX, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. Oncologist. 2010;15(2):168–81.
3. Chan E, Berlin J. Biliary tract cancers: understudied and poorly understood. J Clin Oncol : Off J Am Soc Clin Oncol. 2015;33(16):1845–8.
4. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81.
5. Harstad L, Hess KR, Groves MD. Prognostic factors and outcomes in patients with leptomeningeal melanomatosis. Neuro-Oncology. 2008;10(6):1010–8.
6. Mack F, Baumert BG, Schafer N, et al. Therapy of leptomeningeal metastasis in solid tumors. Cancer Treat Rev. 2016;43:83–91.
7. Kokkoris CP. Leptomeningeal carcinomatosis. How does cancer reach the pia-arachnoid? Cancer. 1983;51(1):154–60.
8. Doval DC, Azam S, Sinha R, Batra U, Mehta A, Rao A. A report of two cases of leptomeningeal carcinomatosis arising from gallbladder carcinoma. J Gastrointest Cancer. 2015;46(4):417–20.
9. Pedrazzoli P, Merlo P, Da Prada GA, Scelsi M, Gatti C, Martelli A. Late onset of gallbladder carcinoma with meningeal carcinomatosis. Eur J Cancer. 1992;28A(8–9):1589.
10. Tans RJ, Koudstaal J, Koehler PJ. Meningeal carcinomatosis as presenting symptom of a gallbladder carcinoma. Clin Neurol Neurosurg. 1993;95(3):253–6.
11. Gaumann A, Marx J, Bohl J, Kommoss F, Kohler H, Tews DS. Leptomeningeal carcinomatosis and cranial nerve palsy as presenting symptoms of a clinically inapparent gallbladder carcinoma. Pathol Res Pract. 1999;195(7):495–9.
12. Goyal S, Mohanti BK. Leptomeningeal dissemination in gall bladder carcinoma: sequelae of long-term survival? Case Rep Hepatol. 2014;2014:717403.
13. Miyagui T, Luchemback L, Teixeira GH, de Azevedo KM. Meningeal carcinomatosis as the initial manifestation of a gallbladder adenocarcinoma associated with a Krukenberg tumor. Revista do Hospital das Clinicas. 2003;58(3):169–72.
14. Honma K, Hamashima H. Fulminating gallbladder cancer presenting as leptomeningeal carcinomatosis and acute renal failure. Wien Klin Wochenschr. 1990;102(21):654–6.
15. Glosova L, Dundr P, Effler J, Ruzickova M. Gallbladder carcinoma cells in cerebrospinal fluid as the first manifestation of a tumor. A case report. Acta Cytol. 2003;47(6):1087–90.
16. Jose N, Perla HT, Iyadurai R, Chacko G. Leptomeningeal carcinomatosis in a patient with gallbladder carcinoma. J Cytol. 2017;34:118–21.
17. Chamberlain M, Soffietti R, Raizer J, et al. Leptomeningeal metastasis: a response assessment in neuro-oncology critical review of endpoints and response criteria of published randomized clinical trials. Neuro-Oncology. 2014;16(9):1176–85.
18. Kim DY, Lee KW, Yun T, et al. Comparison of intrathecal chemotherapy for leptomeningeal carcinomatosis of a solid tumor: methotrexate alone versus methotrexate in combination with cytosine arabinoside and hydrocortisone. Jpn J Clin Oncol. 2003;33(12):608–12.
19. Berg SL, Chamberlain MC. Systemic chemotherapy, intrathecal chemotherapy, and symptom management in the treatment of leptomeningeal metastasis. Curr Oncol Rep. 2003;5(1):29–40.
20. Herrlinger U, Forschler H, Kuker W, et al. Leptomeningeal metastasis: survival and prognostic factors in 155 patients. J Neurol Sci. 2004;223(2):167–78.
21. Morris PG, Reiner AS, Szenberg OR, et al. Leptomeningeal metastasis from non-small cell lung cancer: survival and the impact of whole brain radiotherapy. J Thor Oncol : Off Publ Int Assoc Study Lung Cancer. 2012;7(2):382–5.