

## Diagnosing Primary Malignancy in Leptomeningeal Carcinomatosis by Using CSF Cytology and Immunohistochemistry: A Case Report

### Abstract

We present a rare case of recurrent carcinoma of gallbladder with leptomeningeal carcinomatosis. Cerebrospinal fluid (CSF) cytology showed atypical cells, which were suspicious for malignancy on initial reporting. Diagnosis of malignancy and primary from hepatobiliary source was confirmed by doing immunohistochemistry on CSF cell block.

**Keywords:** Gallbladder carcinoma, immunohistochemistry, leptomeningeal

### Introduction

Among the biliary tract malignancies, gallbladder carcinoma (GBC) is the most common worldwide.<sup>[1]</sup> Compared to southern and western regions, GBC has a higher incidence rate in Northeast and Central India.<sup>[2]</sup> The incidence rate in North India is 10–12/100,000 population which is similar to high incidence countries of South America. The incidence has been raising steadily, while median survival is less than 6 months and 5-year overall survival is less than 5%.<sup>[3]</sup> GBC is an aggressive tumor with early dissemination to regional lymph nodes and liver. At the time of diagnosis, 25% of GBCs are localized to the gallbladder wall, 35% have regional lymph nodal involvement, and 45% have distant metastasis. Although systemic metastasis in GBC is common, the central nervous system (CNS) involvement is rare. The incidence of CNS metastasis from GBC is reported as 2%.<sup>[4]</sup>

We present a case of GBC who received chemotherapy, followed by radical cholecystectomy as with curative intent at another institute. While on follow-up, he presented with leptomeningeal metastasis, which was confirmed by immunohistochemistry (IHC) on cerebrospinal fluid (CSF) cell block.

### Case Report

A 61-year-old man with advanced GBC (gallbladder mass infiltrating into

segment V and noncontiguous lesion in segment VII of the liver) was treated elsewhere with chemotherapy (6 cycles of gemcitabine and cisplatin from May 2018 to December 2018). In September 2018, after 3 cycles of chemotherapy, positron emission tomography–computed tomography (PET-CT) showed partial response. The patient received 3 more cycles of chemotherapy with gemcitabine and cisplatin. In February 2019, he underwent radical cholecystectomy with excision of hepatic lesion. Histopathology showed well-differentiated adenocarcinoma (residual in the gallbladder) ypT1 N0. Later, he was on maintenance chemotherapy with tablet capecitabine for 6 months.

In the last week of March 2020 (6 months after completing maintenance), he came to the emergency department of our hospital with complaints of difficulty in passing urine and constipation, radiating pain in bilateral lower limbs, difficulty in speaking, and hoarseness of voice which was associated with cough while taking food.

On evaluation, magnetic resonance imaging brain and thoraco-lumbo-sacral spine showed heterogeneous hyperintense lesion [Figure 1] in the parasagittal region and patchy dural enhancement in the cervicodorsal region. Videostroboscopy showed left vocal cord palsy. Fluorodeoxyglucose PET-CT ruled out disease at other sites. These findings pointed to bulbar palsy as a possible cause of his hoarseness of voice and dysphagia. The bulbar palsy was likely a result of

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leptomeningeal disease. CSF was planned to confirm the same. CSF showed atypical cells, which were suspicious of malignancy, CSF protein was 266.7 mg/dl, and glucose was 29.4 mg/dl. To confirm the diagnosis and primary, IHC markers were done on cell blocks from CSF [Figure 2]. Cell block from CSF showed malignant cell clusters in Figure 2a and b. CK7-positive cells are in Figure 2c and MUC-1 (Mucin-1, cell surface associated protein (clone MMAB, BioSB))-positive cells in Figure 2d. Cells were negative for CK20 and CDX2. Diagnosis of metastatic adenocarcinoma was confirmed on CSF with strong MUC1 staining favoring pancreatobiliary origin. For dysphagia, nasogastric feeding was started. Intrathecal chemotherapy (IT) was given with methotrexate and hydrocortisone weekly. Post 3 weeks of IT chemotherapy, the patient had symptomatically improved. However, the patient succumbed to chest infection in April 2020.

### Discussion

GBC metastasis to CNS is a rare Phenomenon. The most common manifestation of CNS involvement is leptomeningeal carcinomatosis (LMC).<sup>[5,6]</sup> Symptoms associated with LMC are headache, paresthesia, cranial nerve palsies, radicular pain, alteration in mental status, and cerebellar dysfunction. A combination of clinical examination, neuroimaging, and lumbar puncture (LP) helps in diagnosing LMC.<sup>[7]</sup> The presence of malignant cells in CSF is diagnostic. Other features supporting diagnosis are raised CSF pressure, high protein, low glucose, and pleocytosis. In LMC, CSF protein >45 mg/dl is seen in 63%–90% of patients, CSF pressure >150 mm seen in 30%–57% of patients, pleocytosis seen in 33%–79%, and

decreased glucose levels (<60 mg/dl) seen in 24%–62% of patients.<sup>[8]</sup> In our case, CSF showed atypical cells, which were suspicious of malignancy. Delayed CSF smear preparation is known to alter the cytology picture and hence results in ambiguous reporting. Paucicellularity also results in difficult diagnosis. Establishment of diagnosis is critical for management, and repeat lumbar puncture is generally not favored by patients.

CSF analysis by IHC, fluorescent *in situ* hybridization, polymerase chain reaction, and flow cytometry is known to improve the diagnostic rates. The sensitivity and specificity of IHC in LMC are 0.54 and 0.98, respectively.<sup>[7]</sup> IHC markers done on cell block from CSF in our case clearly established carcinomatosis (CK positive) and also confirmed hepatobiliary primary (MUC1, CK7 positive and CK 20, CDX2 negative).

There are no clear guidelines for the management of LMC. The treatment is mainly palliative either using IT chemotherapy or radiotherapy. Despite these therapies, the prognosis is guarded and ranges from 3 to 6 months.<sup>[9]</sup> Various agents have been employed for use in IT chemotherapy, namely methotrexate, cytarabine, and thiotepa.<sup>[10]</sup>

GBC recurrence with solitary brain metastasis is rare. The case reports of GBC with CNS metastasis with or without other sites of metastasis available in the literature are presented in Table 1.

Patients with solitary brain metastasis with no extracranial involvement have better outcome. Kawamata *et al.*<sup>[11]</sup> reported a case of gall bladder carcinoma metastasis to left cerebellopontine angle with osteolytic changes in left petrous apex mimicking a tentorial meningioma. In Which

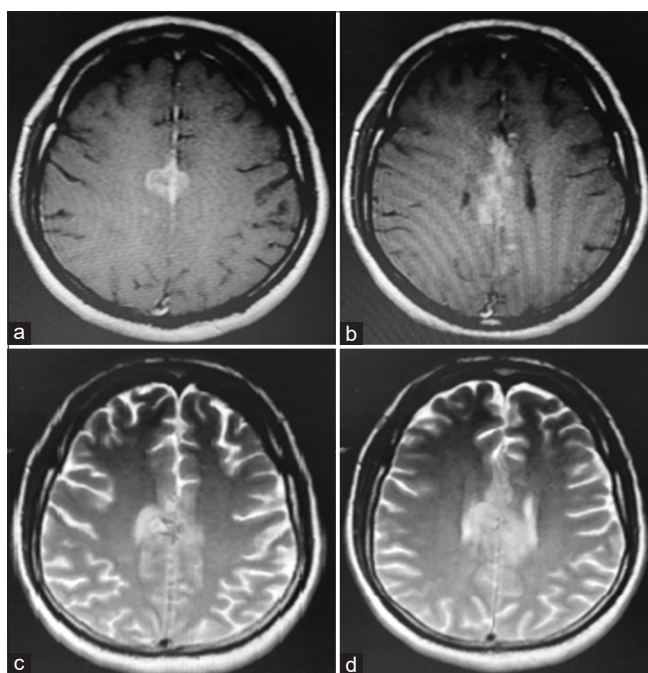


Figure 1: (a and b) T1-weighted images showing intermediate signal lesions. (c and d) T2-weighted images showing hyperintense lesions

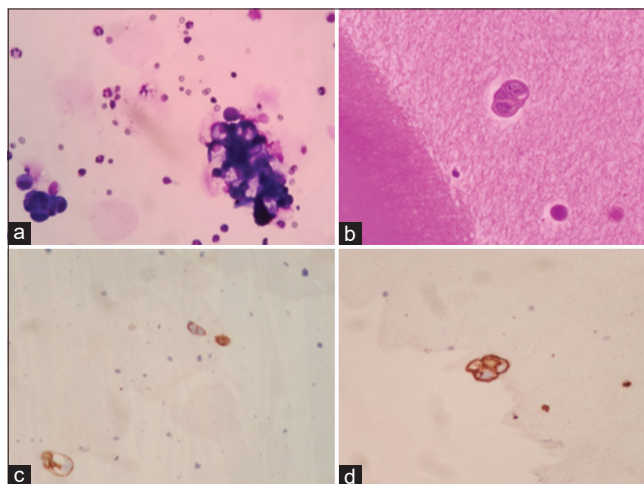


Figure 2: (a) Cytochrome centrifuge smears from cerebrospinal fluid showing few malignant cell clusters in hemorrhagic background (MGG stain, original magnification  $\times 400$ ). (b) Section from cell block reveals only an occasional malignant epithelial cell cluster (H and E stain, original magnification  $\times 400$ ). (c) Immunohistochemistry for CK7 shows positive staining in tumor cells (CK7 immunohistochemistry, original magnification  $\times 400$ ). (d) Immunohistochemistry for MUC1 showing positive staining in tumor cells (MUC1 immunohistochemistry, original magnification  $\times 400$ )

**Table 1: Previous case reports of gall bladder carcinoma with brain metastasis**

Case report	Presentation
Kawamata <i>et al.</i> <sup>[11]</sup>	Left cerebellopontine angle tumor with osteolytic changes in left petrous apex mimicking a tentorial meningioma.
Takano <i>et al.</i> <sup>[12]</sup>	Left frontal cystic lesion.

patient manifested with stroke-like features (sudden onset aphasia, altered sensorium, right hemiparesis, hypertension, right facial nerve palsy, and exaggerated deep tendon reflexes). Takano *et al.*<sup>[12]</sup> reported the case of a 68-year-old female patient with solitary brain metastasis, who after metastasectomy had a survival of 4 years. In patients with multiple metastases, the prognosis is poor and the 5-year overall survival rate is <10%.<sup>[13]</sup>

The unique feature of our case was isolated LMC and confirmation of diagnosis using IHC on CSF cell block. We recommend CSF cell block and IHC for cases not diagnosed on routine cytology. This will require discussion and planning with cytopathologists and technicians. It may also convincingly establish the primary carcinoma where primary is not obvious.

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**Conflicts of interest**

There are no conflicts of interest.

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